Answer 1:

Bibliographic Information

Novel Prodrugs of Tegafur that Display Improved Anticancer Activity and Antiangiogenic Properties. Engel, Dikla; Nudelman, Abraham; Tarasenko, Nataly; Levovich, Inesa; Makarovsky, Igor; Sochotnikov, Segev; Tarasenko, Igor; Rephaeli, Ada. Chemistry Department, Bar-Ilan University, Ramat Gan, Israel. Journal of Medicinal Chemistry (2008), 51(2), 314-323. Publisher: American Chemical Society, CODEN: JMCMAR ISSN: 0022-2623. Journal written in English. CAN 148:205317 AN 2008:15602 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New and more potent prodrugs of the 5-fluorouracil family derived by hydroxymethylation or acyloxymethylation of 5-fluoro-1-(tetrahydro-2-furanyl)-2,4(1H,3H)-pyrimidinedione (Tegafur, 1) are described. The anticancer activity of the butyroyloxymethyl-Tegafur deriv. 3 and not that of Tegafur was attenuated by the antioxidant N-acetylcysteine, suggesting that the increased activity of the prodrug is in part mediated by an increase of reactive oxygen species. Compd. 3 in an in vitro matrigel assay was a more potent antiangiogenic agent than Tegafur. In vivo 3 was significantly more potent than Tegafur in inhibiting 4T1 breast carcinoma lung metastases and growth of HT-29 human colon carcinoma tumors in a mouse xenograft. In summary, the multifunctional prodrugs of Tegafur display selectivity toward cancer cells, antiangiogenic activity, and anticancer activities in vitro and in vivo, superior to those of Tegafur. 5-Fluoro-1-(tetrahydro-2-furanyl)-2,4(1H,3H)-pyrimidinedione (Tegafur, 1), the oral prodrug of 5-FU, has been widely used for treatment of gastrointestinal malignancies with modest efficacy. The aim of this study was to develop and characterize new and more potent prodrugs of the 5-FU family derived by hydroxymethylation or acyloxymethylation of Tegafur. Comparison between the effect of Tegafur and the new prodrugs on the viability of a variety of cancer cell lines showed that the IC50 and IC90 values of the novel prodrugs were 5-10-fold lower than those of Tegafur. While significant differences between the IC50 values of Tegafur were obsd. between the sensitive HT-29 and the resistant LS-1034 colon cancer cell lines, the prodrugs affected them to a similar degree, suggesting that they overcame drug resistance. The increased potency of the prodrugs could be attributed to the antiproliferative contribution imparted by formaldehyde and butyric acid, released upon metabolic degrdn. The anticancer activity of the butyroyloxymethyl-Tegafur deriv.

3 and not that of Tegafur was attenuated by the antioxidant N-acetylcysteine, suggesting that the increased activity of the prodrug is in part mediated by an increase of reactive oxygen species. Compd. 3 in an in vitro matrigel assay was a more potent antiangiogenic agent than Tegafur. In vivo 3 was significantly more potent than Tegafur in inhibiting 4T1 breast carcinoma lung metastases and growth of HT-29 human colon carcinoma tumors in a mouse xenograft. In summary, the multifunctional prodrugs of Tegafur display selectivity toward cancer cells, antiangiogenic activity and anticancer activities in vitro and in vivo, superior to those of Tegafur.

Answer 2:

Bibliographic Information

Benefits of TS-1 plus leucovorin combination therapy for colorectal cancer: evaluation of therapeutic effect of TS-1 and leucovorin combination therapy using rodent model fed a low folate diet. Tsujimoto, Hiroaki; Tsukioka, Sayaka; Koizumi, Katsuhisa; Nakagawa, Fumio; Uchida, Junji; Sugimoto, Yoshikazu; Oka, Toshinori; Fukushima, Masakazu; Watanabe, Toshiaki. Optimal Medication Research Laboratory, Taiho Pharmaceutical Co., Ltd., Japan. Gan to Kagaku Ryoho (2007), 34(3), 413-418. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 147:23014 AN 2007:447767 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We evaluated the therapeutic effect of TS-1, a novel oral fluoropyrimidine, in combination with leucovorin with in vivo expts. using a murine tumor xenograft model fed a low folate diet. The reduced folate levels in the tumors of mice fed a low folate diet were significantly lower than those in the tumors of mice fed a normal diet. In addn., the basal reduced folate levels in the tumors of mice fed a low folate diet were comparable to those in human colorectal cancer tissues. Furthermore, when leucovorin was orally

administered, the reduced folate levels in the tumors of mice fed a low folate diet were more than two-fold higher than those of mice fed the normal diet. The leucovorin-induced potentiation of TS-1 antitumor activity was obviously higher in COL-1 tumor-bearing mice fed a low folate diet than in mice fed a normal diet. The remarkable increase in reduced folate levels following the administration of leucovorin contributed to the leucovorin-induced potentiation of TS-1 antitumor activity in this low-folate-diet animal model. These results suggest that rodent models fed a low folate diet are suitable for in vivo evaluation of reduced folate drugs like leucovorin. In this model, the combination of leucovorin with TS-1 resulted in a higher antitumor efficacy than TS-1 alone or the combination of UFT and leucovorin, suggesting that TS-1 and leucovorin combination therapy may be an effective regimen for patients with colorectal cancer.

Answer 3:

Bibliographic Information

Amrubicin, a novel 9-aminoanthracycline, enhances the antitumor activity of chemotherapeutic agents against human cancer cells in vitro and in vivo. Hanada, Mitsuharu; Noguchi, Toshihiro; Yamaoka, Takashi. Pharmacology Research Laboratories, Drug Research Division, Dainippon Sumitomo Pharma Co., Ltd, 3-1-98, Kasugadenaka, Konohana-ku, Osaka, Japan. Cancer Science (2007), 98(3), 447-454. Publisher: Blackwell Publishing Asia Pty Ltd., CODEN: CSACCM ISSN: 1347-9032. Journal written in English. CAN 146:266424 AN 2007:262575 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Amrubicin, a completely synthetic 9-aminoanthracycline deriv., is an active agent in the treatment of untreated extensive disease-small-cell lung cancer and advanced non-small-cell lung cancer. Amrubicin administered i.v. at 25 mg/kg substantially prevented the growth of five of six human lung cancer xenografts established in athymic nude mice, confirming that amrubicin as a single agent was active in human lung tumors. To survey which antitumor agent available for clin. use produces a synergistic interaction with amrubicin, we examd. the effects in combinations with amrubicinol, an active metabolite of amrubicin, of several chemotherapeutic agents in vitro using five human cancer cell lines using the combination index (CI) method of Chou and Talalay. Synergistic effects were obtained on the simultaneous use of amrubicinol with cisplatin, irinotecan, gefitinib and trastuzumab, with CI values after 3 days of exposure being <1. Additive effect was obsd. with the combination contg. vinorelbine with CI values indistinguishable from 1, while the combination of amrubicinol with gemcitabine was antagonistic. All combinations tested in vivo were well tolerated. The combinations of cisplatin, irinotecan, vinorelbine, trastuzumab, tegafur/uracil, and to a lesser extent, gemcitabine with amrubicin caused significant growth inhibition of human tumor xenografts without pronouncedly enhancing body wt. loss, compared with treatment using amrubicin alone at the max. tolerated dose. Growth inhibition of tumors by gefitinib was not antagonized by amrubicin. These results suggest that amrubicin appears to be a possible candidate for combined use with cisplatin, irinotecan, vinorelbine, gemcitabine, tegafur/uracil or trastuzumab.

Answer 4:

Bibliographic Information

Changes to the dihydropyrimidine dehydrogenase gene copy number influence the susceptibility of cancers to 5-FU-based drugs: Data mining of the NCI-DTP data sets and validation with human tumour xenografts. Kobunai, Takashi; Ooyama, Akio; Sasaki, Shin; Wierzba, Konstanty; Takechi, Teiji; Fukushima, Masakazu; Watanabe, Toshiaki; Nagawa, Hirokazu. Department of Systematic Clinical Oncology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan. European Journal of Cancer (2007), 43(4), 791-798. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:1058 AN 2007:213726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Patient response to the anti-tumor drug 5-fluorouracil (5-FU) is variable, but predicting the response rate is important for the selection of effective chemotherapy. Our aim was to identify alterations in DNA copy no. that influence susceptibility of cancer cells to 5-FU-based drugs. The NCI public database was used to identify chromosome loci assocd. with drug sensitivity and DNA copy no.

One of the 11 candidates, the cytogenetic band 1p21.3, harbors the dihydropyrimidine dehydrogenase (DPD) gene. To validate this finding, the DPD copy no. and in vivo sensitivity to 5-FU-based drugs were detd. in 31 human tumor xenografts. Those xenografts demonstrating low sensitivity had significantly higher DPD copy nos. than highly sensitive tumors ($P < 0.002$). Moreover, DPD mRNA expression levels were significantly correlated with DPD copy nos. ($P < 0.046$). An assessment of copy no. may be a more precise method of predicting the sensitivity of cancer patients to 5-FU related drugs.

Answer 5:

Bibliographic Information

Antimetastatic and anticancer activity of S-1, a new oral dihydropyrimidine-dehydrogenase-inhibiting fluoropyrimidine, alone and in combination with paclitaxel in an orthotopically implanted human breast cancer model. Nukatsuka, Mamoru; Fujioka, Akio; Nakagawa, Fumio; Oshimo, Hideyuki; Kitazato, Kenji; Uchida, Jyunji; Sugimoto, Yoshikazu; Nagayama, Sekio; Fukushima, Masakazu. Applied Oncology Section, Postmarketing Research Laboratory, Taiho Pharmaceutical Co., Ltd., Tokushima, Japan. International Journal of Oncology (2004), 25(6), 1531-1536. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 142:254003 AN 2005:14775 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To evaluate the antitumor and antimetastatic efficacy of oral fluoropyrimidines, alone and combined with taxane on human breast cancer xenografts model, we developed a breast cancer model that spontaneously metastasizes to the lung by orthotopic implantation of MDA-MB-435S-HM tumors into the mammary fat pad (mfp) of SCID mice. The activity of the 5-fluorouracil (5-FU)-degrading enzyme dihydropyrimidine dehydrogenase (DPD) was significantly higher in the metastatic tumors than in the primary tumors. Based on this enzymic characteristic of pulmonary metastases of breast cancer in regard to 5-FU metab., we investigated the antitumor activity of two types of oral 5-FU prodrugs, with and without paclitaxel, on both orthotopically implanted breast tumors and metastatic lung tumors in mice. The drugs and doses used were: S-1, a new oral DPD-inhibiting fluoropyrimidine (DIF) 8.3 mg/kg/day, capecitabine 360 mg/kg/day as a non-DIF, and paclitaxel 50 mg/kg, all of which display minimal toxicity in mice. In the primary tumors, paclitaxel and S-1 displayed a significant antitumor activity, with 57 and 41%, resp. inhibition of tumor growth ($p<0.01$), but capecitabine had no effect. When S-1 and paclitaxel were combined, they synergistically caused tumor regression (tumor growth inhibition ratio 94%, $p<0.01$) in mice compared to capecitabine plus paclitaxel, without any toxicity. In the pulmonary metastasis model, paclitaxel, and both S-1 alone and combined with paclitaxel, but not capecitabine alone or combined with paclitaxel, displayed almost complete antimetastatic activity. These results strongly suggest that combination of S-1, as a DIF with taxanes will show a potent high antitumor and antimetastatic effect on refractory human breast cancers, esp. those expressing strong DPD activity.

Answer 6:

Bibliographic Information

Dependence of chemotherapy response on p53 mutation status in a panel of human cancer lines maintained in nude mice. Koike, Masako; Fujita, Fumiko; Komori, Kinuyo; Katoh, Fumitaka; Sugimoto, Takuji; Sakamoto, Yasuo; Matsuda, Masato; Fujita, Masahide. Experimental Cancer Chemotherapy Research Laboratory Co., Ltd., Osaka, Japan. Cancer Science (2004), 95(6), 541-546. Publisher: Japanese Cancer Association, CODEN: CSACCM ISSN: 1347-9032. Journal written in English. CAN 141:343028 AN 2004:613610 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In contrast to findings in vitro, the clin. response to anticancer chemotherapy is not simply assocd. with the p53 mutation status. To analyze the relation between the actual response of solid tumors with p53 mutation and other biol. characteristics, we used a human cancer-nude mouse panel of 21 lines derived from stomach, colorectal, breast, lung, and liver cancers for exptl. chemotherapy. We examd. the tumor growth rates of the cancer lines and the effects of nine drugs in clin. use, namely, mitomycin C (MMC), cisplatin (CDDP), nimustine hydrochloride (ACNU), irinotecan (CPT-11), cyclophosphamide (CPA), 1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207),

a 4:1 mixt. of uracil and FT-207 (UFT), 5'-deoxy-5-fluorouridine (5'-DFUR), and adriamycin (ADM), on these tumors. The chemotherapy response was expressed as the tumor growth inhibition rate (IR). The genomic DNA sequences of the p53 gene in exons 5 through 8 were analyzed in these cancer tissues, and p53 mutations were detected in 10 of the 21 cancer lines (48%). Resistance to MMC was obsd. in p53 mutant tumors with smaller IRs than those for wild-type tumors (57.7% vs. 79.9%, P<0.03). No significant differences were noted with the other eight drugs. To explore the role of the p53 function in the chemotherapy response, we calcd. the correlation coeffs. between chemosensitivity and tumor growth rate sep. in p53 mutant and wild-type groups. In the p53 wild-type group, we found a pos. correlation for the following drugs: ADM (P<0.02), ACNU (P<0.007), CPA (P<0.011), UFT (P<0.012), and FT-207 (P<0.02). In the p53 mutant group, only CPA (P<0.003) showed a pos. correlation. The kinetics suggests that in the wild-type tumors, DNA damage caused by anticancer drugs occurs proportionally to the rate of DNA synthesis, and p53-mediated apoptosis is subsequently induced. The low frequency of pos. correlation in the p53 mutant tumors is compatible with the loss of function or malfunction of mutant p53.

The present results provide kinetic evidence that p53 function affects the response to anticancer drugs. Preserved p53 function tended to confer good chemosensitivity on rapidly growing tumors. However, the p53 mutation status did not seem to be suitable for use as an exclusive indicator to predict the chemotherapy response of human cancer xenografts.

Answer 7:

Bibliographic Information

Combined effects of docetaxel and fluoropyrimidines on tumor growth and expression of interleukin-6 and thymidine phosphorylase in breast cancer xenografts. Yamamoto, Shigeru; Kurebayashi, Junichi; Kurosumi, Masafumi; Kunisue, Hironori; Otsuki, Takemi; Tanaka, Katsuhiro; Sonoo, Hiroshi. Department of Breast and Thyroid Surgery, Kawasaki Medical School, Kurashiki, Okayama, Japan. Cancer Chemotherapy and Pharmacology (2001), 48(4), 283-288. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 137:87924 AN 2001:695783 CAPLUS

Abstract

Although several combination treatments with docetaxel and other antitumor agents have been tested in exptl. and clin. studies, their synergistic effects are still ill-defined. The degree of synergism between docetaxel and two oral fluoropyrimidines, Tegafur and 5'-deoxy-5-fluorouridine (5'-dFUrd), was investigated in the KPL-4 human breast cancer xenograft model. Because this KPL-4 cell line secretes interleukin-6 (IL-6) and induces cachexia, the effects of the combined treatment on serum IL-6 levels and cachectic markers were investigated. In addn., the expression levels of thymidine phosphorylase (dThdPase), a key enzyme for converting 5'-dFUrd to 5-fluorouracil, were detd. Female nude mice bearing KPL-4 tumors were treated orally with 5'-dFUrd (60 mg/kg, five times a week) or Tegafur (100 mg/kg, five times a week) and by i.p. injection of docetaxel (5 or 10 mg/kg, once a week). Although docetaxel (5 mg/kg) alone did not decrease either tumor growth or serum IL-6 levels, docetaxel (5 mg/kg) plus 5'-dFUrd or Tegafur enhanced tumor growth inhibition and decreased serum IL-6 levels more than 5'-dFUrd or Tegafur alone. Docetaxel (5 mg/kg) alone slightly increased the percentage of dThdPase-pos. tumor cells, but the combined treatment with docetaxel plus 5'-dFUrd or Tegafur significantly decreased the percentage of dThdPase-pos. cells in the KPL-4 tumors. These findings indicate that docetaxel may stimulate dThdPase expression in tumor tissues and may enhance the antitumor activity of oral fluoropyrimidines. In addn., combined treatment with docetaxel and oral fluoropyrimidines may decrease serum IL-6 levels and may ameliorate IL-6-induced cancer cachexia.

Answer 8:

Bibliographic Information

Induction of apoptosis in human tumor xenografts after oral administration of uracil and Tegafur to nude mice bearing tumors. Oki, E.; Sakaguchi, Y.; Toh, Y.; Oda, S.; Maehara, Y.; Yamamoto, N.; Sugimachi, K. Cancer Centre, Kyushu University Hospital, Tokushima, Japan. British Journal of Cancer (1998), 78(5), 625-630. Publisher: Churchill Livingstone, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 129:339518 AN 1998:584309 CAPLUS

Abstract

Various types of anti-neoplastic agents induce apoptosis in vitro, but less is known of the role of this mode of cell death in tumors treated in vivo. We examd. the induction of apoptosis by oral anti-neoplastic agents, Tegafur and uracil (UFT, a combined prepn. of 1 mol Tegafur and 4 mol uracil), and the relation of effects on tumor growth. Seven different human gastrointestinal tumor xenografts were transplanted into nude mice, including two colon adenocarcinomas (KM20C and Col-1), three gastric carcinomas (SC-6, St-40 and 4-1ST) and two pancreatic carcinomas (PAN-4 and PAN-12), followed by oral administration of UFT (24 mg kg-1 day-1) for 9 days. The percentage of apoptotic cells in each tumor was scored in histol. sections, chronol., using a mol. biol.-histochem. system and growth inhibition was examd. in each tumor. A significant growth inhibition by UFT was obsd. for all tumors, except PAN-12. In KM20C and SC-6, growth inhibition rates were 61.7% and 60.6% resp. Quant. assay for apoptosis showed a remarkable induction of apoptosis in KM20C (4.2%) and SC-6 (3.5%), which were relatively sensitive to UFT. In addn., KM20C and SC-6 showed a higher incidence of spontaneous apoptosis. In five other tumors, which responded to a lesser extent than KM20C and SC-6, UFT altered little the changes in apoptosis (less than 2%) and spontaneous apoptosis was relatively low. Thus, tumors with a higher apoptosis induced by UFT had a higher response to UFT. Apoptosis obsd. in tumors might serve as a predictor of a preferable response to UFT.

Answer 9:

Bibliographic Information

Predictability of clinical response to anticancer agents in human cancer xenografts. Tsukamoto, Fumine. Med. Sch., Osaka Univ., Suita, Japan. Osaka Daigaku Igaku Zasshi (1994), 46(4), 251-61. CODEN: ODIZAK ISSN: 0369-710X. Journal written in Japanese. CAN 121:124753 AN 1994:524753 CAPLUS

Abstract

Nude mouse transplanted human tumors retained original sensitivity to antitumor drugs, and was useful in secondary screening for the sensitivity to tumor chemotherapy. Fresh tumor tissues were transplanted and maintained in nude mice in 77 cases (tried: 247 cases), and sensitivity of the transplanted tumors to chemotherapy was compared between human therapy and in nude mice using regimen used clin. in 17 cases with 21 expts. (stomach, breast, colon, pancreas, esophagus. melanoma). Tested drugs were adriamycin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, doxifluoridine, epirubicin, 5-fluorouracil, M-83 (a mitomycin C deriv.), mitomycin C, tegafur, and UFT. Chemotherapy in nude mice was effective in 6 expts., which coincided with clin. results in 5 cases. The ineffective 15 cases in nude mice coincided with the clin. results in all cases.

Answer 10:

Bibliographic Information

A pharmacodynamic and pharmacokinetic study of fluoropyrimidines in a nude mouse system and in postoperative patients with gastric cancer. Inada, Takao; Ogata, Yoshiro; Kubota, Tetsuro; Ozawa, Iwao; Hishinuma, Shoichi; Shimizu, Hideaki; Kotake, Kenjiro; Ikeda, Tadashi; Koyama, Yasuo. Dep. Surg., Tochigi Cancer Cent., Tochigi, Japan. Surgery Today (1993), 23(8), 687-92. CODEN: SUTOE5 ISSN: 0941-1291. Journal written in English. CAN 119:216687 AN 1993:616687 CAPLUS

Abstract

To evaluate the effect of the oral fluoropyrimidines, tegafur and uracil (UFT) and 5-fluorouracil (5-FU), a pharmacodynamic anal. was conducted using a nude mouse system and patients. In the nude mouse system, UFT and 5-FU showed similar marginal effects against the human tumor xenograft Co-J, and the concn. of 5-FU in serum 1 h after the last administration being 0.04 μg/mL, which was assumed to be the min. effective concn. (MEC). Postoperative patients were subdivided into three groups, being: those who underwent subtotal gastrectomy and received UFT; those who underwent subtotal gastrectomy and received 5-FU; and those who underwent total gastrectomy and received UFT. In the UFT groups, the concn. of 5-FU in the portal and peripheral blood showed similar elimination in terms of the peak concn. (Cmax) and the area under the curve (AUC). In the 50FU groups, the AUC and Cmax were significantly higher in portal blood than peripheral blood. The concns. in the portal blood of the 5-FU group and in the portal and peripheral blood of the UFT group were significantly higher than the MEC (0.04 μg/mL). From these pharmacodynamic data, it was

concluded that postoperative chemotherapy with oral fluoropyrimidines can achieve the MEC in portal and peripheral blood.

Answer 11:

Bibliographic Information

Predictability of preclinical evaluation of anticancer drugs by human gastrointestinal cancer-nude mouse panel. Fujita, Masahide; Fujita, Fumiko; Sakamoto, Yasuo; Sugimoto, Takuji; Shimozuma, Kojiro; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Suita, Japan. Gan to Kagaku Ryoho (1991), 18(9), 1429-37. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 115:269825 AN 1991:669825 CAPLUS

Abstract

The predictability of clin. responses to anticancer agents was studied using a human cancer-nude mouse panel. The human cancer lines used were 12 gastric, 4 colorectal, 3 breast, 2 pancreatic cancers and 1 melanoma xenografted into BALB/c athymic nude mice. Treatment was conducted daily 25 times for antimetabolites, and intermittently 5 times once or twice a week for other drugs. The dosage of each drug was the maximal tolerated dose predetd. for the treatment and schedule. Four weeks after the initiation of treatment, the therapeutic effect was evaluated by the tumor growth inhibition rate (IR) based on the mean tumor wt. When the IR was >58%, the drug was evaluated as effective. The clin. response rate of each drug was referred from the result of a phase II study. Direct comparison of antitumor effects on 16 tumor xenografts with responses to the corresponding clin. therapy of each donor patient revealed a fairly high accordance rate (94%). To elucidate the value of human cancer-nude mouse panel as a preclin. secondary screening, the response rates to 8 anticancer drugs used in 15 cancer xenografts were compared with the cumulative clin. data available for each drug. Generally, the response rates of the human cancer xenografts to the drugs showed fairly good correlations with the cumulative clin. response rates to the corresponding drugs in the same organs. Using this panel, preclin. examns. of 6 new agents under development, including 254-S and 2 cisplatin derivs., were performed in order to collect clin. data.

Answer 12:

Bibliographic Information

In vivo inhibitory effect of anticancer agents on human pancreatic cancer xenografts transplanted in nude mice. Imai, Shiro; Nio, Yoshinori; Shiraishi, Takahiro; Manabe, Tadao; Tobe, Takayoshi. Fac. Med., Kyoto Univ., Kyoto, Japan. Anticancer Research (1991), 11(2), 657-64. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 115:174179 AN 1991:574179 CAPLUS

Abstract

Pancreatic cancer is one of the neoplasms resistant to chemotherapy. In the present study human pancreatic cancer xenografts (3 adenocarcinomas and 1 cystoadenocarcinoma) were s.c. transplanted in nude mice and after the tumors grew to 100-300 mm3, the mice were i.p. administered with mitomycin C (MMC), adriamycin (ADR), 5-fluorouracil (5-FU), carboquone (CQ), cisplatinum (CDDP), nimustine chloride (ACNU) or DWA2114R at 1/3 LD50 on days 0, 4, and 8. The tumor sizes on day 12 were compared with those on day 0. MMC and CQ significantly inhibited the tumor growth of 3 lines, and ACNU, CDDP and ADR inhibited the growth of 1 line. Further, 5-FU, futrafur, carmofur, UFT, and L-phenylalanine mustard (L-PAM) were orally administered to mice into which 1 adenocarcinoma line had been transplanted. While none of fluoropyrimidines inhibited tumor growth, L-PAM at 4 mg/kg significantly inhibited growth, although it was accompanied by severe body wt. loss. In the present study several agents significantly inhibited tumor growth, but none of them could induce the regression of the tumor when used singly. These results suggest that CQ, ACNU, CDDP and L-PAM may be applied to the chemotherapy of pancreatic cancer. However, the effect of a single agent is restricted and the development of new combination treatments is urgently required.

Answer 13:

Bibliographic Information

Epidermal growth factor receptor-mediated selective cytotoxicity of antitumor agents toward human xenografts and murine syngeneic solid tumors. Amagase, Harunobu; Kakimoto, Masanori; Hashimoto, Ken; Fuwa, Tohru; Tsukagoshi, Shigeru. Inst. Med. Res., Wakunaga Pharm. Co., Ltd., Hiroshima, Japan. Japanese Journal of Cancer Research (1989), 80(7), 670-8. CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 111:126597 AN 1989:526597 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In a dose-dependent manner, human EGF enhanced the efficacy of an antitumor agent (5-FU) treatment against human epidermoid carcinoma A431 transplanted s.c. in athymic nude mice. Various degrees of enhancement were also obsd. against other exptl. tumors transplanted s.c. The degrees of enhancement were directly proportional to the nos. of human EGF binding sites present on tumor cell plasma membrane (threshold of binding site d. = 1.5 × 103 sites/cell) using 5-FU or cisplatin as an antitumor agent, thus suggesting that the binding of EGF to the receptors on tumor cells is an essential process in enhancing the susceptibility of tumor cells to antitumor agents. Normal cells including intestinal epithelial and bone marrow cells are endowed with fewer EGF binding site (<103 sites/cell). This may partially explain the absence of EGF-enhanced cytotoxicity by antitumor agents toward normal cells.

Answer 14:

Bibliographic Information

Combined effects of interferon α-A/D with fluoropyrimidine derivatives in subrenal capsule assay. Nishiyama, Masahiko; Takagami, Shinichi; Kirihara, Yoshimasa; Saeki, Toshiaki; Niimi, Ken; Kim, Ryungsa; Jinushi, Kazuto; Toge, Tetsuya; Niimoto, Minoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Gan to Kagaku Ryoho (1988), 15(8), 2285-90. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 109:204561 AN 1988:604561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Synergistic, additive, or subadditive antitumor effects were obsd. following the combined administration of interferon α-A/D with fluoropyrimidine derivs. (i.e., 5-FU, tegafur, and 5'-deoxy-5-fluorouridine, UFT, and 1-hexylcarbamoyl-5-fluorouracil) to athymic mice bearing human tumor xenografts (H-111 and SH-10 gastric cancers and CH-5 colon cancer). The combinations were not effective against CH-4 colon cancer of human.

Answer 15:

Bibliographic Information

Antitumor effect of UFT on human ovarian cancer grafted in nude mice and 5-FU concentration in the tumor and normal tissues. Yoshiya, Norio; Adachi, Shigemi; Misawa, Yoshio; Ishida, Michio; Yuzawa, Hideo; Kanazawa, Koji; Takeuchi, Shoshichi. Sch. Med., Niigata Univ., Niigata, Japan. Gan to Kagaku Ryoho (1988), 15(2), 285-9. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 108:179762 AN 1988:179762 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antitumor effects of UFT, tegafur (FT-207), cisplatin (CDDP) and the combination of UFT with CDDP were studied in a human ovarian cancer xenograft in nude mice and the concn. of 5-fluorouracil (5-FU) was detd. in the tumor tissue and major organs. UFT (48.6 mg/kg/day) or tegafur (15.0 mg/kg/day) was administered for 20 days, orally, and CDDP (5 mg/kg/day) was administered i.p. each 7th day for 3 wk. The inhibitions of the tumor growths were 49.6% with UFT, -2.3% with tegafur, and 17.7% with CDDP. With the combination of UFT and CDDP, severe side effects were obsd. The concn. of 5-FU in the UFT-treated group was higher than that in the tegafur group: .apprx.2 times in the tumor, 5 times in the liver, 9 times in the kidneys and 4 times in the spleen. The concns of 5-FU in the major organs, esp. in the kidneys, in nude mice that died 10 days after UFT plus CDDP administration were higher than in

those of mice receiving only UFT. UFT increases the intratumoral concn. of 5-FU to elicit better antitumor effects and also increases the concn. of 5-FU in various normal organs after long-term administration.

Answer 16:

Bibliographic Information

Evaluation by multiple regression analysis of factors influencing the chemosensitivity of human tumors xenografted into nude mice. Fujita, Fumiko; Fujita, Masahide; Hirai, Toshihiro; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1987), 14(3, Pt. 1), 618-25. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 107:17103 AN 1987:417103 CAPLUS

Abstract

The chemosensitivity of human cancer lines is thought to be a result of contributions of various interacting factors. Multiple regression analyses were performed in order to clarify the weighting of factors responsible for the chemosensitivity of 15 human cancers xenografted into nude mice. Inhibition rates of 11 anticancer agents, predetd. sep. for each cancer line, were used as the criterion variables. As the explanatory variables, 9 parameters characteristic of each cancer or cancer-bearing mouse were selected as follows: grade of differentiation, vascularity, percentage of necrosis, vol. doubling time, labeling index, lactic dehydrogenase (LDH) activity, tissue/serum LDH ratio, thymidine phosphorylase activity, and serum carcinoembryonic antigen. By applying this anal. with stepwise deletion, the estd. multiple regression equations for drug sensitivity were detd. for each drug. Although all equations were composed of different factors and their partial inhibition coeffs. varied from drug to drug, the equations for analogous drugs such as FT-207 and UFT, or mitomycin C and M-83, had similar factors. The equations for M-83, ACNU, and adriamycin consisted of a no. of parameters with a sufficiently high coeff. of detn. of 80%. Even for drugs such as methotrexate, that showed no significant factor upon simple correlation anal., an equation with 7 factors revealed a coeff. of detn. of 0.83. The estd. values of effectiveness of these drugs showed marked coincidence with the actual values. For some drugs, the in vivo mode of action was inferred through this anal.

Answer 17:

Bibliographic Information

In vivo chemosensitivity test for UFT and FT-207. I. Subrenal capsule assay. Nishiyama, Masahiko; Niimi, Ken; Yamaguchi, Masahiro; Hirabayashi, Naoki; Nosoh, Yoshihiro; Tohge, Tetsuya; Niimoto, Monoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Gan to Kagaku Ryoho (1987), 14(1), 109-13. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 106:149093 AN 1987:149093 CAPLUS

Abstract

A chemosensitivity test for UFT [74578-38-4] and FT-207 (tegafur) [17902-23-7], which are used in long-term administration clin., was investigated for prediction of the clin. response. Five transplantation-established human tumor xenograft systems were examd. using the subrenal capsule assay. Both anticancer agents showed antiproliferative effects according to the total administered dose. Two of 5 tumors were detd. to be sensitive to UFT using microscopic measurements following intragastric administration of 1/2 of the LD50 value, while they were shown to be resistant to 5-FU. In these 2 cases, prolongation of life span by long-term administration of UFT was shown clin. All these expts. could be performed if the loss of body wt. in mice was less than 20%. Apparently, in the 4-day subrenal capsule assay, clin. responses to long-term administration of UFT or FT-207 are predictable using intragastric high-dose administration which does not induce more than 20% body wt. loss in mice.

Answer 18:

Bibliographic Information

Chemosensitivity of human gastrointestinal and breast cancer xenografts in nude mice. Fujita, Fumiko; Fujita, Masahide; Kimoto, Yasuhiko; Shimozuma, Kojiro; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1985), 12(2), 353-61. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 102:160155 AN 1985:160155 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Exptl. chemotherapies for 15 human cancers xenografted into nude mice were performed using 14 anticancer agents including 6 drugs in clin. use. Treatment with each single agent was performed for every cancer line using the max. tolerated dose following continuous daily (antimetabolites) or intermittent (cytocidal agents) schedules. Generally, the exptl. results for each drug on the xenografts was in good accordance with the known clin. effects of each drug on the same type of cancer. On the other hand, individual cancer xenografts showed considerable differences in chemosensitivity. Some tumors were sensitive to a majority of the drugs, whereas some were resistant to many of them. Each cancer line seemed to retain individuality in its spectrum of chemosensitivity irresp. of whether it derived from the same organ or whether it was of similar histol. type. Apparently, selection of drugs is necessary for a specific type of tumor.

Answer 19:

Bibliographic Information

Experimental chemotherapy with fluoropyrimidine compounds on human gastrointestinal and breast cancers xenografted to athymic nude mice. Fujita, Masahide; Fujita, Fumiko; Nakano, Yosuke; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. International Congress Series (1984), 647(Fluoropyrimidines Cancer Ther.), 121-32. CODEN: EXMDA4 ISSN: 0531-5131. Journal written in English. CAN 102:142866 AN 1985:142866 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In treatment of nude mice bearing human gastrointestinal and breast cancer xenografts with antitumor drugs (25-30 mg/kg/day), tegafur [17902-23-7] was effective in 6 out of 15 human cancer lines (40%) and uracil-tegafur mixt. (UFT) [74578-38-4] and 5'-deoxy-5-fluorouridine (5'DFUR) [3094-09-5] were both effective in 11 out of 15 lines (73%). Among the 3 drugs, 5'DFUR led the most frequently to the shrinkage of treated tumors.

Answer 20:

Bibliographic Information

Chemosensitivity of human gastrointestinal and breast cancer xenografts in nude mice and predictability to clinical response of anticancer agents. Fujita, M.; Fujita, F.; Taguchi, T. Dep. Oncol. Surg., Osaka Univ., Osaka, Japan. Editor(s): Sordat, Bernard. Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res., 4th (1984), Meeting Date 1982, 311-15. Publisher: Karger, Basel, Switz CODEN: 51ONAB Conference written in English. CAN 101:103450 AN 1984:503450 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effectiveness of 13 drugs against 14 lines of human gastrointestinal and breast cancers xenografted in nude mice was studied. Despite identical origins of organ and similarities in histol. types, degrees of differentiation, and growth rate, each line of cancer demonstrated different spectra of sensitivity to various agents. The effectiveness of various chemotherapeutic agents against human gastric cancer xenografts in nude mice was compared with the clin. effects of these drugs in clin. trials and phase II studies. The results indicated that the nude mouse-human cancer system would be useful in preclin. secondary screening.

Answer 21:

Bibliographic Information

Anticancer effectiveness of the combined administration of ftorafur and uracil. Taguchi, Tetsuo. Univ. Osaka, Osaka, Japan. Eksperimental'naya i Klinicheskaya Farmakoterapiya (1983), 12 205-14. CODEN: EKFMA7 ISSN: 0367-0589. Journal written in Russian. CAN 100:167831 AN 1984:167831 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor effectiveness of combination therapy with ftorafur (I) [17902-23-7] and uracil (II) [66-22-8] was evaluated against the tumor lines S-180 and AH-130, as well as spontaneous mammary carcinoma, in SHN mice, and against xenografts of human cancers in nude mice. Oral administration of I and II increased the concns. of 5-fluorouracil [51-21-8] in the tumors and in the blood. In clin. studies, I + II therapy was quite effective, the treatment being well tolerated by the patients.

Answer 22:

Bibliographic Information

Comparative data from experimental chemotherapy of human tumor xenografts in nude mice, and the clinical responses of the patient-donors. Taguchi, Tetsuo; Fujita, Masahide. Univ. Osaka, Osaka, Japan. Eksperimental'naya i Klinicheskaya Farmakoterapiya (1983), 12 77-83. CODEN: EKFMA7 ISSN: 0367-0589. Journal written in Russian. CAN 100:167828 AN 1984:167828 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A high degree of correlation was found between the effects of ftorafur [17902-23-7] in combination with MFC (mitomycin C [50-07-7], 5-fluorouracil [51-21-8], and cytosine arabinoside [147-94-4]) on the growth of tumor xenografts of 3 different human tumors in nude mice and the effects of the same chemotherapy on the patient-donors of the cell lines.

Answer 23:

Bibliographic Information

Antitumor efficacy of seventeen anticancer drugs in human breast cancer xenograft (MX-1) transplanted in nude mice. Inoue, Katsuhiro; Fujimoto, Shuichi; Ogawa, Makoto. Div. Clin. Chemother., Cancer Chemother. Cent., Tokyo, Japan. Cancer Chemotherapy and Pharmacology (1983), 10(3), 182-6. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 99:98704 AN 1983:498704 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activity of 17 anticancer drugs was studied in the treatment of a human breast cancer tumor (MX-1) transplanted into nude mice. The antitumor activity of the drugs was evaluated at the LD10 predetd. in mice as a std. therapeutic dose. Drugs were administered i.v., i.p., or orally, and antitumor activity was assessed by drug-induced growth inhibition measured by calipers. Among the 17 anticancer drugs, the most active compds. (max. inhibition of rate of tumor growth: ≥90%) are mitomycin C, chromomycin A3, vincristine, vinblastine, vindesine, and hexamethylmelamine. Another group of compds. showed moderate activity (max. inhibition rate of tumor growth: 89%-50%), these being adriamycin, daunomycin, mitoxantrone, bleomycin, 5-fluorouracil, 6-thioguanine, and ftorafur. The remaining 4 drugs (peplomycin, cytosine arabinoside, 6-mercaptopurine, and methotrexate) were inactive against the MX-1 tumor. These results suggest that in the nude mouse-human tumor xenograft system there is a good correlation between the antitumor activity of various anticancer drugs and their clin. efficacy; this system is therefore expected to be a useful model for secondary screening.

Answer 24:

Bibliographic Information

New method for evaluating the effect of experimental chemotherapy on human xenografts in nude mice: use of lactate dehydrogenase isozyme. Hayata, Satoshi; Fujita, Masahide; Nakano, Yosuke; Kumagai, Michihiko; Hakozaki, Michinori; Taguchi, Tetsuo. Res. Inst. Microbial Dis., Osaka Univ., Osaka, Japan. Editor(s): Periti, Piero; Gialdroni Grassi, Giuliana. Curr. Chemother. Immunother., Proc. Int. Congr. Chemother., 12th (1982), Meeting Date 1981, 2 1283-4. Publisher: Am. Soc. Microbiol., Washington, D. C CODEN: 48HGAR Conference written in English. CAN 97:174303 AN 1982:574303 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Monitoring human lactate dehydrogenase (I) [9001-60-9] isozyme 5 during chemotherapy in the nude mouse was more sensitive than conventional methods for evaluation of treatment. In H-55 (gastric) and H-62 (breast) tumors, good correlation between tumor vols. and human I were obsd. and the coeffs. were 0.686 and 0.803, resp. H-81 gastric cancer was very sensitive to TA-077 [70189-62-7] (100 mg/kg, weekly). S.c. tumor decreased after treatment and almost disappeared at the termination of the expt. Human I also decreased, and this decrease was greater than that obsd. for tumor size. The I isozyme method was more sensitive than the measurement of tumor size. In the ascitic tumor (Br-13 breast cancer) system, the effect of drugs was easily detd. by the human I level.

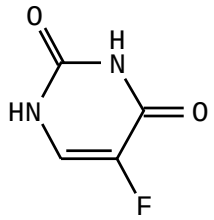
Answer 25:

Bibliographic Information

Immunobiology and therapeutic manipulation of heterotransplanted Nb rat prostatic adenocarcinoma. Chemotherapy of autonomous tumor, 102 Pr, heterotransplanted into congenitally athymic (nude) mice and syngeneic Nb rats. Drago, Joseph R.; Maurer, Robert E.; Goldman, Laurence B.; Gershwin, M. Eric. Sch. Med., Univ. California, Davis, CA, USA. Cancer Chemotherapy and Pharmacology (1979), 3(3), 167-70. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 92:69573 AN 1980:69573 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Chemotherapy of Nb rat prostatic adenocarcinoma, autonomous tumor, 102 Pr, with 5-fluorouracil (I) [51-21-8] and Ftorafur (II) [17902-23-7] had similar effects on tumor progression in both nude mice (lacking functional T cells) and Nb rats. I was more efficacious than II in both species. Data showing differences in growth vs. time in the resp. recipient animal hosts is presented. The combination animal model system could be used for screening potential cytotoxic chemotherapeutic agents.



I

Answer 26:

Bibliographic Information

Combination therapy of S-1 with selective cyclooxygenase-2 inhibitor for liver metastasis of colorectal carcinoma. Tachimori Akiko; Yamada Nobuya; Amano Ryosuke; Ohira Masaichi; Hirakawa Kosei Department of

Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan Anticancer research (2008), 28(2A), 629-38. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 18507001 AN 2008344245 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Hepatic resection, the only curative treatment for liver metastasis of colorectal cancer has become standard treatment, but most cases of liver metastases are inoperable, and of the patients treated with hepatectomy about 50% have a recurrence in the liver. The aim of this study was to establish preventive therapy for the liver metastasis of colorectal cancer. MATERIALS AND METHODS: In this study, a combined treatment with S-1 and a selective COX-2 inhibitor for liver metastasis of colorectal cancer was developed. The effect of these agents on the proliferation and invasion of a highly metastatic human colon cancer cell line, LM-H3, was examined. RESULTS: 5-Fluorouracil (5-FU) had an inhibitory effect on the proliferation of LM-H3 cells, but no inhibitory effect on the invasion of LM-H3 cells in in vitro experiments. 5-Chloro-2,4-dihydroxypyridine (CDHP) had no antitumor activity itself, but the inhibitory effect of 5-FU on the proliferation was enhanced by adding CDHP. COX-2 inhibitors, etodolac and rofecoxib, did not have an inhibitory effect on the proliferation of LM-H3 cells at low concentrations, but had significant inhibitory effect on the invasion of LM-H3 cells in in vitro experiments. In a nude mouse liver metastasis model, combined treatment with S-1 and a COX-2 inhibitor more effectively restrained liver metastasis of LM-H3 cells than either alone. This outcome was most likely due to S-1 inhibiting proliferation of and the COX-2 inhibitor inhibiting invasion of LM-H3 cells. CONCLUSION: Combined therapy with S-1 and a COX-2 inhibitor might hold promise for prophylaxis of liver metastasis of colorectal cancer.

Answer 27:

Bibliographic Information

Pretreatment with S-1, an oral derivative of 5-fluorouracil, enhances gemcitabine effects in pancreatic cancer xenografts. Nakahira Shin; Nakamori Shoji; Tsujie Masanori; Takeda Setsuo; Sugimoto Keishi; Takahashi Yuji; Okami Jiro; Marubashi Shigeru; Miyamoto Atsushi; Takeda Yutaka; Nagano Hiroaki; Dono Keizo; Umeshita Koji; Sakon Masato; Monden Morito Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, E2, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan Anticancer research (2008), 28(1A), 179-86. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18383843 AN 2008226058 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: The systemic administration of gemcitabine (GEM) has been accepted as a standard treatment for patients with advanced pancreatic cancer. The major mediator of cellular uptake of GEM is the human equilibrative nucleoside transporter 1 (hENT1) whose expression is up-regulated by thymidylate synthase inhibitors, such as 5-fluorouracil (5-FU). S-1 is a novel oral derivative of the 5-FU prodrug tegafur combined with two modulators. Recent clinical trials have reported the promising effect of S-1 in pancreatic cancer. The purpose of this study was to evaluate the relationship between different schedules and the effects of GEM/S-1 combination therapy on pancreatic cancer xenograft models. MATERIALS AND METHODS: Human pancreatic tumor xenografts were prepared by subcutaneous implantation of MiaPaCa-2 into nude mice. Expression of hENT1 was determined by quantitative RT-PCR. GEM cellular uptake was determined using [3H] GEM. RESULTS: Significant increases in hENT1 expression and GEM cellular uptake were observed after S-1 treatment. Six different treatment schedules (no treatment, single agent of GEM or S-1, combination treatment with GEM either before, simultaneously or following administration of S-1) were compared. Significant tumor growth inhibition was observed in the mice treated with S-1 followed by GEM compared to either untreated mice or the mice treated with the other schedules. CONCLUSION: Based on the effects of S-1 on the uptake of GEM, S-1 should be used before GEM treatment. The GEM/S-1 combination therapy in patients with pancreatic cancer may be promising and should be tested in clinical trials.

Answer 28:

Bibliographic Information

On the development of models in mice of advanced visceral metastatic disease for anti-cancer drug testing.
Man Shan; Munoz Raquel; Kerbel Robert S Department of Molecular and Cellular Biology Research, Sunnybrook Health Sciences Centre, S-217, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5, Canada Cancer metastasis reviews (2007), 26(3-4), 737-47. Journal code: 8605731. ISSN:0167-7659. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T); General Review; (REVIEW) written in English. PubMed ID 17846863 AN 2007669179 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

It is well known clinically that advanced, bulky visceral metastatic disease is generally much less responsive to most anti-cancer therapies, compared to microscopic metastatic disease. This problem is exacerbated when treating cancers that have been previously exposed to multiple lines of therapy, and which have acquired a 'refractory' phenotype. However, mimicking such clinical treatment situations in preclinical mouse models involving the testing of new or existing cancer therapies is extremely rare. Treatment of 'metastasis', in retrospect, usually involves minimal residual disease and therapy naive tumors. This could account in many instances for the failure to reproduce highly encouraging preclinical results in subsequent phase I or phase II clinical trials. To that end, we have embarked on an experimental program designed to develop models of advanced, visceral metastatic disease, in some cases involving tumors previously exposed to various therapies. The strategy first involves the orthotopic transplantation of a human cancer cell line, such as breast cancer cell line, into the mammary fat pads of immune deficient mice, followed by surgical resection of the resultant primary tumors that develops. Recovery of distant macroscopic metastases, usually in the lungs, is then undertaken, which can take up to 4 months to visibly form. Cell lines are established from such metastases and the process of orthotopic transplantation, surgical resection, and recovery of distant metastases is undertaken, at least one more time. Using such an approach highly metastatically aggressive variant sublines can be obtained, provided they are once again injected into an orthotopic site and the primary tumors removed by surgery. By waiting sufficient time after removal of the primary tumors, about only 1 month, mice with extensive metastatic disease in sites such as the lungs, liver, and lymph nodes can be obtained. An example of therapy being initiated in an advanced stage of such disease development is illustrated.

Metastases that eventually stop responding to a particular therapy can be removed as a source of variant cell lines which have both 'refractory' and highly metastatic phenotypes. Such models may provide a more accurate picture of the potential responsiveness to an experimental therapy so that a high degree of responsiveness observed could be a factor in deciding whether to move a particular therapy forward into phase I/phase II clinical trial evaluation. An example of this is illustrated using doublet metronomic low-dose chemotherapy for the treatment of advanced metastatic breast cancer, using two conventional chemotherapy drugs, namely, cyclophosphamide and UFT, a 5-FU oral prodrug.

Answer 29:

Bibliographic Information

Investigation of optimal schedule of concurrent radiotherapy with S-1 for oral squamous cell carcinoma.
Harada Koji; Ferdous Tarannum; Yoshida Hideo Department of Therapeutic Regulation for Oral Tumors, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima 770-8504, Japan. harako@dent.tokushima-u.ac.jp Oncology reports (2007), 18(5), 1077-83. Journal code: 9422756. ISSN:1021-335X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 17914556 AN 2007593095 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In the present study, we examined the appropriate schedule of S-1 medication in the combination with radiation by investigating the safety, the clinical efficacy, and antitumor effects on tumors in nude mice. In the patients with oral squamous cell carcinoma (OSCC), S-1 was given orally according to a 4-week application followed by 2-week rest regimen (4-week regimen), or a 2-week application followed by a 1-week rest regimen (2-week regimen). Radiation was given (2 Gy/day; 5 days/week) for a total of 60 Gy. In nude mouse models, human oral cancer cell lines were used as subcutaneous xenografts in nude mice. The mice were treated by S-1 (10 mg/kg) and radiation (1 Gy) with a 4-week regimen or a 2-week regimen. Apoptotic cells were detected by TUNEL method. In the patients with OSCC, the response rate with the 4-week regimen was 100% and the response rate with the 2-week regimen was 92.3%. However, a high frequency of adverse effect was found in the 4-week regimen when compared to the 2-week regimen. Grade 3 toxicity of leukopenia, neutropenia and stomatitis were seen in 3 cases, grade 3 toxicity of anorexia and nausea were seen in 2 cases, and grade 3 toxicity of decrease of hemoglobin level, heartburn/dyspepsia and increase of bilirubin level were seen in a case of the 4-week regimen. On the other hand, grade 3 toxicity of stomatitis, anorexia, nausea, heartburn/dyspepsia and increase of bilirubin level were seen in a case of the 2-week regimen. In nude mouse models, the 2-week regimen was more effective than the 4-week regimen. In addition, significant increase in the percentage of apoptotic cells was observed in the tumors treated with the 4-week regimen when compared with the tumors treated with the 2-week regimen. No loss of body weight was observed in mice treated with the 2-week regimen during the experimental period. These results suggested that the 2-week regimen might reduce adverse effects, and enhance therapeutic effects compared to the 4-week regimen.

Briefly, this 2-week regimen may be a useful concurrent chemo-radiotherapy improving the quality of life (QOL) of patients with OSCC.

Answer 30:

Bibliographic Information

Enhancement of antitumor effect of tegafur/uracil (UFT) plus leucovorin by combined treatment with protein-bound polysaccharide, PSK, in mouse models. Katoh Ryoji; Ooshiro Mitsuru Department of Surgery, Toho University Sakura Medical Center, Sakura-shi, Chiba, Japan. ryochan@sakura.med.toho-u.ac.jp Cellular & molecular immunology (2007), 4(4), 295-9. Journal code: 101242872. ISSN:1672-7681. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 17764620 AN 2007515747 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We evaluated the antitumor effect of combined therapy with tegafur/uracil (UFT) plus leucovorin (LV) (UFT/LV) and protein-bound polysaccharide, PSK, in three mouse models of transplantable tumors. UFT/LV showed antitumor effect against Meth A sarcoma, and the antitumor effect was enhanced when PSK given concomitantly. UFT/LV showed antitumor effect to Lewis lung carcinoma and PSK alone also showed antitumor effect at high dose, but a combination of UFT/LV and PSK resulted in no enhanced antitumor effect. Colon 26 carcinoma was weakly responsive to UFT/LV, and no enhancement of antitumor effect was found even PSK was used in combination. In conclusion, while the effect of PSK varies depending on tumor, combined use of UFT/LV and PSK may be expected to augment the antitumor effect.

Answer 31:

Bibliographic Information

Effects of tumor necrosis factor-related apoptosis-inducing ligand alone and in combination with fluoropyrimidine anticancer agent, S-1, on tumor growth of human oral squamous cell carcinoma xenografts in nude mice. Itashiki Yasutaka; Harada Koji; Ferdous Tarannum; Yoshida Hideo Department of Therapeutic Regulation for Oral Tumors, Institute of Health Bioscience, University of Tokushima Graduate School, Tokushima, Japan Anticancer research (2007), 27(4B), 2365-75. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 17695527 AN 2007477167 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Chemotherapy has shown little antitumor activity against advanced oral squamous cell carcinoma (OSCC) patients. Therefore, there is an urgent need to develop more effective therapeutic methods for patients with advanced OSCC. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a member of the tumor necrosis factor ligand family that selectively induces apoptosis of cancer cells. S-1 is a new oral antineoplastic agent that can induce apoptosis in various types of cancer cells, including OSCC. Hence, combined treatment of cancer cells with TRAIL and S-1 might exert dramatic antitumor effects on OSCC cells. MATERIALS AND METHODS: In this study, the response of human OSCC cells to TRAIL alone and in combination with S-1 was examined using nude mouse xenograft models. S-1 (10 mg/kg/day, 5 times/week) was administered orally and TRAIL (1 mg/kg, 5 times/week) was injected into peritumoral tissue for three weeks. Apoptotic cells were detected by a TUNEL method. The protein expression of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and orotate phosphoribosyl transferase (OPRT) were assessed using immunohistochemistry; their gene expression was determined using microdissection and RT-PCR, and their protein levels using ELISA. RESULTS: Combined therapy of TRAIL and S-1 exerted antitumor effects on human OSCC xenografts markedly and significantly induced apoptotic cells in tumors treated with TRAIL plus S-1. Immunohistochemistry showed that the expressions of TS and DPD were down-regulated, and that OPRT expression was up-regulated in tumors treated with TRAIL plus S-1. In the same way, microdissection and RT-PCR revealed that the expression of TS and DPD mRNA was down-regulated and that expression of OPRT mRNA was up-regulated in tumors administered the combined treatment. Moreover, ELISA indicated that the protein levels of TS and DPD were down-regulated, and that OPRT was up-regulated in tumors treated with the combined therapy.

During the experimental period, no loss of body weight was observed in mice treated with the combined therapy. CONCLUSION: These findings demonstrate that the combination of TRAIL and S-1 is effective against OSCC and has the potential of being a new therapeutic tool for future treatment of these tumors.

Answer 32:

Bibliographic Information

Antitumor activity of a combination of trastuzumab (Herceptin) and oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2-overexpressing pancreatic cancer. Saeki Hiroyuki; Yanoma Shunsuke; Takemiya Shouji; Sugimasa Yukio; Akaike Makoto; Yukawa Norio; Rino Yasushi; Imada Toshio Department of General Surgery, Yokohama City University, Kanagawa 236-0004, Japan. saekihiroyuki@yahoo.co.jp Oncology reports (2007), 18(2), 433-9. Journal code: 9422756. ISSN:1021-335X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 17611667 AN 2007393496 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The cytotoxic effect of trastuzumab in combination with oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2 (HER2)-overexpressing human pancreatic cancer cell line TRG in vitro and in vivo was investigated. HER2 expression in TRG was analyzed by RT-PCR and flow cytometry. For in vitro experiments, 5-fluorouracil (5-FU) was used instead of S-1. In vivo studies were conducted with TRG xenografts in athymic mice. Trastuzumab (10 mg/kg) was administered intraperitoneally once a week for 4 weeks. S-1 (10 mg/kg) was administered orally 5 days a week for 4 weeks. The results showed that TRG cells were positive for HER2 mRNA and overexpressed HER2 protein. Either trastuzumab or 5-FU concentration-dependently inhibited the growth of TRG cells. The combination of trastuzumab and 5-FU resulted in a significant inhibition of growth of TRG cells compared to either agent alone ($P<0.001$). Incubation of TRG cells with peripheral blood mononuclear cells after treatment with trastuzumab enhanced the antiproliferative effect of trastuzumab, which could be the result of antibody-dependent cellular cytotoxicity. The combination of trastuzumab and S-1 resulted in a significant reduction in xenograft volume compared to each agent alone ($P<0.0001$). In conclusion, this study showed that combination therapy with trastuzumab and S-1 may be effective for HER2-overexpressing pancreatic cancer patients.

Answer 33:

Bibliographic Information

Antitumor activity and function of S-1, a new oral tegafur-based formulation. Fukushima Masakazu Tokushima Research Center, Taiho Pharmaceutical Co., Ltd., Japan Gan to kagaku ryoho. Cancer & chemotherapy (2006), 33 Suppl 1 19-26. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 16897968 AN 2006474322 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

TS-1 (S-1), developed by the scientific theory of both potentiating antitumor activity of 5-fluorouracil (5-FU) and reducing gastrointestinal toxicity induced by 5-FU, is a new oral formulation consisting of 1 M tegafur, 0.4 M gimeracil and 1 M oteracil potassium. We investigated the antitumor efficacy of S-1 alone and in combination with other cytotoxic anticancer drugs using subcutaneously or orthotopically implanted murine and human tumors in rodents. As a single agent, S-1 showed higher antitumor activity with its low intestinal toxicity compared to continuous venous infusion 5-FU, the most effective dosing method of 5-FU, and/or to clinically available oral fluoropyrimidines such as UFT, doxyfluridine and capecitabine on various murine tumors and human tumor xenografts. Especially, it was noteworthy that S-1 as a DPD-inhibitory fluoropyrimidine markedly affected human tumor xenografts with high expression levels of DPD on which other fluoropyrimidines showed a low antitumor activity. In combination with other anticancer drugs such as CPT-11 and taxanes, S-1 exercised synergistic antitumor efficacy not only on 5-FU-sensitive tumors with low expression levels of thymidylate synthase (TS) but also on 5-FU-resistant tumors with originally higher and/or elevated levels of TS expression. As one of the reasonable mechanism of antitumor synergism by the combination, CPT-11 and taxanes were found to reduce the expression of TS in human tumor resistant to 5-FU with high expression TS levels. Throughout our preclinical antitumor studies of S-1, alone and/or in combination with other anticancer drugs, it would be expected to contribute greatly to the treatment of cancer patients.

Answer 34:

Bibliographic Information

Schedule-dependent therapeutic effects of gemcitabine combined with uracil-tegafur in a human pancreatic cancer xenograft model. Tsujie Masanori; Nakamori Shoji; Nakahira Shin; Takeda Setsuo; Takahashi Yuji; Hayashi Nobuyasu; Okami Jiro; Nagano Hiroaki; Dono Keizo; Umeshita Koji; Sakon Masato; Monden Morito Department of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, E2, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan Pancreas (2006), 33(2), 142-7. Journal code: 8608542. E-ISSN:1536-4828. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16868479 AN 2006445366 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

OBJECTIVES: Gemcitabine is taken up by cells mainly via human equilibrative nucleoside transporter 1 (hENT1). Pretreatment of cancer cell lines with 5-fluorouracil (5-FU) leads to an increase in the expression of hENT1 and augments the effect of single-agent gemcitabine treatment in vitro. The purpose of the present study was to evaluate the relationship between the schedules of gemcitabine/uracil-tegafur (UFT) combination therapy and their effects in pancreatic cancer in vivo. METHODS: The expression level of hENT1 mRNA was examined using 6 types of human pancreatic cancer cell lines treated with 5-FU and MiaPaCa-2 xenograft tumors in BALB/c nu/nu mice treated with UFT. A [H] gemcitabine cellular uptake assay was performed using MiaPaCa-2 cells treated with 5-FU. We compared the effects of 6 different schedules of treatment using UFT and/or gemcitabine on MiaPaCa-2 xenograft tumors. RESULTS: MiaPaCa-2 cell line was one of the lines that showed the highest rate of 5-FU-induced increase in the hENT1 mRNA level. Gemcitabine uptake was significantly increased when cells were treated with 5-FU. Treatment with UFT significantly increased the hENT1 mRNA expression in MiaPaCa-2 tumors. A significant growth inhibition of MiaPaCa-2 tumors was observed in the mice treated with UFT followed by gemcitabine as compared with either untreated mice or UFT

alone-treated mice. CONCLUSIONS: Our results suggest that the schedule in which the gemcitabine is administered after UFT may be the optimal combination for gemcitabine/UFT treatment in pancreatic cancer.

Answer 35:

Bibliographic Information

S-1, an oral fluoropyrimidine, enhances radiation response of DLD-1/FU human colon cancer xenografts resistant to 5-FU. Nakata Eiko; Fukushima Masakazu; Takai Yoshihiro; Nemoto Kenji; Ogawa Yoshihiro; Nomiya Takuma; Nakamura Yasuhiro; Milas Luka; Yamada Shogo Tohoku University Biomedical Engineering Research Organaization, Miyagi 980-8575, Japan Oncology reports (2006), 16(3), 465-71. Journal code: 9422756. ISSN:1021-335X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16865244 AN 2006441749 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

S-1, a novel oral fluoropyrimidine, is increasingly used for the treatment of human cancer including gastrointestinal carcinomas. Using the 5-FU resistant DLD-1/FU human colon cancer cell xenografts, the present study investigated whether S-1 enhances the therapeutic efficacy of radiation and if so what are the underlying mechanisms. Nude mice bearing tumor xenografts were treated with radiation, S-1, or both. Tumor growth delay was the treatments' endpoint. To determine whether S-1 enhances intrinsic cell radiosensitivity, we performed clonogenic cell survival assay. Also we assessed the expression of thymidylate synthase (TS) using immunohistochemistry assay. While S-1 or 5 Gy were only slightly effective as single agents in delaying tumor growth, the combined treatment was highly effective. Clonogenic cell survival showed that S-1 strongly enhanced cell radiosensitivity. Immunohistochemistry showed that the expression of TS was down-regulated in tumors treated by S-1 plus radiation. Combined S-1 plus radiation treatment resulted in a synergistic effect in the therapy of 5-FU resistant human colon carcinoma xenografts (EF = 2.06). The effect could be attributed to the ability of S-1 to increase cell radiosensitivity (EF = 1.9) and to the down-regulation of TS involved in cellular processes leading to radio- and (or) chemo-resistance.

Answer 36:

Bibliographic Information

Synergistic effects of docetaxel and S-1 by modulating the expression of metabolic enzymes of 5-fluorouracil in human gastric cancer cell lines. Wada Yoshiyuki; Yoshida Kazuhiro; Suzuki Takahisa; Mizuiri Hirozumi; Konishi Kazuo; Ukon Kei; Tanabe Kazuaki; Sakata Yu; Fukushima Masakazu Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan International journal of cancer. Journal international du cancer (2006), 119(4), 783-91. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16557585 AN 2006346720 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We have recently demonstrated in a Phase I/II study that combination chemotherapy with docetaxel (TXT) and S-1 is active against metastatic gastric carcinomas. To elucidate the mechanisms underlying the synergistic effects of these drugs, both the growth inhibitory effects and the expression profiles of enzymes involved in fluorouracil (5-FU) metabolism were examined in vitro and in vivo. TXT alone and in combination with 5-FU inhibited the growth of each of the 5 gastric cancer cell lines that we examined (TMK-1, and MKN-1, -28, -45 and -74), in a time- and dose-dependent manner. Moreover, striking synergistic effects were observed in TMK-1 cells in vitro with IC50 values of between 4.73 and 0.61 nM 5-FU. Furthermore, in TMK-1 xenografts, 5-FU/TXT cotreatments exhibited synergistic antitumor effects. The combination of S-1 and TXT, however, exhibited greater growth-inhibitory effects than the 5-FU/TXT cotreatments. The mechanisms underlying these synergistic effects of S-1 and TXT were examined by expression and activity analyses

of the 5-FU metabolic enzymes. The expression of thymidylate synthase (TS), and dihydropyrimidine dehydrogenase (DPD) were decreased 50 and 73% of control levels, respectively, and that of orotate phosphorybosyl transferase (OPRT) was increased by 3.9-fold at the protein level. These findings suggested that biochemical modulation of the 2 drugs had occurred, which was further confirmed by the results of the activity assays. These data strongly indicate that a combination chemotherapy of TXT and S-1 is effective against gastric carcinomas and is therefore a good candidate as a standard chemotherapeutic strategy in treating these tumors. Copyright 2006 Wiley-Liss, Inc.

Answer 37:

Bibliographic Information

Antitumor effect of combination of S-1 and docetaxel on the human breast cancer xenograft transplanted into SCID mice. Suto Akihiko; Kubota Tetsuro; Fukushima Masakazu; Ikeda Tadashi; Takeshita Toshio; Ohmiya Harumi; Kitajima Masaki Department of Surgery Yamato Municipal Hospital, 8-3-6 Fukami-nishi, Yamato City Kanagawa 242-8602, Japan. akihiko.sutou@city.yamato.lg.jp Oncology reports (2006), 15(6), 1517-22. Journal code: 9422756. ISSN:1021-335X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16685389 AN 2006260882 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In vivo experiments were performed on breast cancer xenografts to examine whether the combination therapy with S-1, an oral dihydrouracil dehydrogenase (DPD) inhibitory fluoropyrimidine, plus docetaxel functions as an additive/synergistic modulator in tumor growth. The human breast cancer xenograft, MDA-MB-435SHM, was inoculated into SCID female mice. The tumor growth and thymidylate synthase (TS)/DPD activity of tumors treated with the agents were investigated. The T/C value (relative mean tumor weight of the treated group/relative tumor weight of the control group) of the group treated with docetaxel, S-1 and combination therapy were 45.3, 63.1 and 29.8%, respectively; suggesting the positive antitumor effects of the combination therapy in particular. In addition, significant down-regulation of DPD activity was also observed in the tumors treated with S-1, docetaxel and their combination. Down-regulation of the DPD activity of the tumors is also considered to be correlated with the antitumor effect of the treated groups, suggesting its influence on the synergistic effect of the combination therapy.

Answer 38:

Bibliographic Information

Experimental chemotherapy against human esophageal carcinoma xenografts with TS-1, cisplatin and docetaxel. Yamada Takaya; Masuda Asako; Tongu Miki; Hiraku Osamu; Etou Tadahiro; Sasaki Ken; Atsuda Koichiro; Morinaga Seijiro; Suzuki Tatsuo; Suzuki Yukio; Osaku Masayoshi; Miyagawa Takeshi; Asanuma Fumiki; Yamada Yoshinori Biomedical Laboratory, Kitasato Institute Hospital Gan to kagaku ryoho. Cancer & chemotherapy (2006), 33(4), 479-85. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 16612157 AN 2006205309 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Three strains of human esophageal carcinoma xenografts established in our institution were tested against combination chemotherapy in vivo and in vitro. TS-1 plus cisplatin (CDDP) was shown to be an effective combination against two carcinoma strains of moderately-differentiated type. Determination of the thymidylate synthase (TS) demonstrated a higher inhibition of the enzyme by adding CDDP to 5-FU, suggesting biochemical modulation. The remaining strain of poorly-differentiated type was resistant to the combination and an attempt was made to add docetaxel (DTX) to show that the three-drug combination was effective against the strain. Combination chemotherapy including TS-1 and CDDP thus appears to be useful treatment choice for esophageal carcinoma.

Answer 39:

Bibliographic Information

Highly efficacious nontoxic preclinical treatment for advanced metastatic breast cancer using combination oral UFT-cyclophosphamide metronomic chemotherapy. Munoz Raquel; Man Shan; Shaked Yuval; Lee Christina R; Wong John; Francia Giulio; Kerbel Robert S Sunnybrook and Women's College Health Sciences Centre S-217, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5 Cancer research (2006), 66(7), 3386-91. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16585158 AN 2006186865 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Metronomic antiangiogenic chemotherapy, the prolonged administration of relatively low drug doses, at close regular intervals with no significant breaks, has been mainly studied at the preclinical level using single chemotherapeutic drugs, frequently in combination with a targeted antiangiogenic drug, and almost always evaluated on primary localized tumors. We tested a "doublet" combination metronomic chemotherapy treatment using two oral drugs, UFT, a 5-fluorouracil (5-FU) prodrug administered by gavage, and cyclophosphamide, for efficacy and toxicity in a new mouse model of advanced, terminal, metastatic human breast cancer. The optimal biological dose of each drug was first determined by effects on levels of circulating endothelial progenitor cells as a surrogate marker for angiogenesis, which was assessed to be 15 mg/kg for UFT and 20 mg/kg for cyclophosphamide. A combination treatment was then evaluated in mice with advanced metastatic disease using a serially selected metastatic variant of the MDA-MB-231 breast cancer-cell line, 231/LM2-4. UFT or cyclophosphamide treatment showed only very modest survival advantages whereas a combination of the two resulted in a remarkable prolongation of survival, with no evidence of overt toxicity despite 140 days of continuous therapy, such that a significant proportion of mice survived for over a year. In contrast, this striking therapeutic effect of the combination treatment was not observed when tested on primary orthotopic tumors. We conclude that combination oral low-dose daily metronomic chemotherapy, using cyclophosphamide and UFT, is superior to monotherapy and seems to be a safe and highly effective experimental antimetastatic therapy, in this case, for advanced metastatic breast cancer.

Answer 40:

Bibliographic Information

Correlations between antitumor activities of fluoropyrimidines and DPD activity in lung tumor xenografts. Takechi Teiji; Okabe Hiroyuki; Ikeda Kazumasa; Fujioka Akio; Nakagawa Fumio; Ohshimo Hideyuki; Kitazato Kenji; Fukushima Masakazu Cancer Research Laboratory, Product Lifecycle Management Department, Taiho Pharmaceutical Co., Ltd., 1-27 Kanda-Nishikicho, Chiyoda-ku, Tokyo 101-8444, Japan. ttakechi@taiho.co.jp Oncology reports (2005), 14(1), 33-9. Journal code: 9422756. ISSN:1021-335X. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15944764 AN 2005298641 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The purposes of this study were to evaluate the antitumor activity of S-1 (1 M tegafur, 0.4 M 5-chloro-2,4-dihydroxypyridine and 1 M potassium oxonate) on human lung tumor xenografts, as compared with other fluoro-pyrimidines, and to investigate the relationships between fluoropyrimidine antitumor activities and four distinct enzymatic activities involved in the phosphorylation and degradation pathways of 5-fluorouracil (5-FU) metabolism. S-1, UFT (1 M tegafur-4 M uracil), 5'-deoxy-5-fluorouridine (5'-DFUR), capecitabine and 5-FU were administered for 14 consecutive days to nude mice bearing lung tumor xenografts. S-1 showed stronger tumor growth inhibition in four of the seven tumors than the other drugs. Cluster analysis, on the basis of antitumor activity, indicated that S-1/UFT and 5'-DFUR/capecitabine/5-FU could be classified into another group. We investigated tumor thymidylate synthase content,

dihydropyrimidine dehydrogenase (DPD) activity, thymidine phosphorylase (TP) activity and orotate phosphoribosyl transferase activity in seven human lung tumor xenografts and performed regression analyses for the antitumor activities of fluoropyrimidines. There were inverse correlations between antitumor and DPD activities for 5'-DFUR (r=-0.79, P=0.034), capecitabine (r=-0.56, P=0.19) and 5-FU (r=-0.86, P=0.013). However, no such correlations were observed for S-1 and UFT. These findings suggest that S-1 containing a potent DPD inhibitor may have an antitumor effect on lung tumors, with high basal DPD activity, superior to those of other fluoropyrimidines.

Answer 41:

Bibliographic Information

Schedule-dependent synergism of vinorelbine and 5-fluorouracil/UFT against non-small cell lung cancer. Matsumoto Shingo; Igishi Tadashi; Hashimoto Kiyoshi; Kodani Masahro; Shigeoka Yasushi; Nakanishi Hirofumi; Touge Hirokazu; Kurai Jun; Makino Haruhiko; Takeda Kenichi; Yasuda Kazuhito; Hitsuda Yutaka; Shimizu Eiji Division of Medical Oncology and Molecular Respirology, Faculty of Medicine, Tottori University, 36-1 Nishimachi, Yonago 683-8504, Japan International journal of oncology (2004), 25(5), 1311-8. Journal code: 9306042. ISSN:1019-6439. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15492820 AN 2004521219 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Elderly patients with advanced non-small cell lung cancer (NSCLC) require chemotherapy that is effective and minimally toxic. We evaluated the activity of a combination of vinorelbine and 5-fluorouracil (5-FU)/UFT (a fixed combination of tegafur and uracil) in vitro and in vivo to establish a rationale for clinical use. The cytotoxic activities of various combinations of vinorelbine and 5-FU, the active metabolite of tegafur, were analyzed by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazlium bromide (MTT) assay and isobologram technique in vitro, using 3 NSCLC cell lines (A549, PC14, and Ma10). Sequential exposure to vinorelbine followed by 5-FU showed additive or synergistic activity against all 3 NSCLC cell lines tested. The reverse sequence showed no synergism. Antitumor activity and survival prolongation after treatment with different combinations of vinorelbine and UFT were evaluated in nude mice bearing PC14 xenografts. Treatment with vinorelbine before UFT was associated with higher antitumor activity, less toxicity, and longer survival than the reverse sequence. To clarify the underlying mechanism by which the combination exerts the synergistic effects, the expression of thymidylate synthase (TS) was assessed by Western blot analysis in vitro and by immunohistochemical analysis in an animal model. Vinorelbine suppressed the 5-FU-induced increase in TS protein in A549 cells. In PC14 tumor tissues of animal models, TS expression in cancer cells was suppressed by vinorelbine. Our data suggest that treatment with vinorelbine injection before oral UFT may have synergistic activity against NSCLC. This synergistic activity may be attributed to increased chemosensitivity to UFT caused by vinorelbine-induced suppression of TS.

Answer 42:

Bibliographic Information

Combined effects of the oral fluoropyrimidine anticancer agent, S-1 and radiation on human oral cancer cells. Harada Koji; Kawaguchi Shin-ichi; Supriatno; Onoue Tomitaro; Yoshida Hideo; Sato Mitsunobu Second Department of Oral and Maxillofacial Surgery, School of Dentistry, University of Tokushima, 3-18-15 Kuramoto-cho, 770-8504, Japan. harako@dent.tokushima-u.ac.jp Oral oncology (2004), 40(7), 713-9. Journal code: 9709118. ISSN:1368-8375. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15172641 AN 2004274675 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We evaluated the orally administered S-1, in combination with ionizing radiation both in vivo and in vitro against human

oral cancer cell lines. Human oral cancer cell lines were used as subcutaneous xenografts in nude mice. S-1 (10 mg/kg) was administered orally 1 h before radiation treatments (1.5 Gy), or 1 h after radiation for five consecutive days. Apoptotic cells were detected by TUNEL method. For in vitro analysis, attached cells were treated with S-1 (50 microg/ml) for 1 h and then irradiated (3, 6, 9, 12, 15 Gy), or they were treated with S-1 for 1 h after radiation. Cell survival was determined by clonogenic assay. The combination of S-1 and radiation was more effective than either agent alone. In addition, S-1 administration before radiation was more effective than S-1 administration after radiation. Moreover, the combination of S-1 and radiation could induce apoptosis significantly than either agent alone ($P < 0.01$). In vitro clonogenic survival experiments demonstrated the dose enhancement ratio of 1.22 (radiation + S-1), 1.45 (S-1 + radiation) in B88 cells, and 1.16 (radiation + S-1), 1.28 (S-1 + radiation) in HSG cells. These data demonstrate that the combination of S-1 and fractionated radiotherapy is more effective against human oral cancer xenografts than either agent alone, and that S-1 administration before radiation is more effective than after radiation, suggesting a potential clinical applicability of combination treatment of S-1 and radiation in oral cancer therapies.

Answer 43:

Bibliographic Information

Superior antitumour activity of S-1 in tumours with a high dihydropyrimidine dehydrogenase activity. Fujiwara H; Terashima M; Irinoda T; Takagane A; Abe K; Nakaya T; Yonezawa H; Oyama K; Takahashi M; Saito K; Takechi T; Fukushima M; Shirasaka T Department of Surgery 1, Iwate Medical University, 020-8505, Morioka, Japan European journal of cancer (Oxford, England : 1990) (2003), 39(16), 2387-94. Journal code: 9005373. ISSN:0959-8049. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 14556932 AN 2003479090 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

To elucidate the mechanism of the enhanced antitumour activity of S-1 (1 M tegafur, 0.4 M 5-chloro-2, 4-dihydroxypyridine, and 1 M potassium oxonate) in terms of the phosphorylation and degradation pathways of 5-fluorouracil (5-FU) metabolism, we investigated tumoral thymidylate synthase (TS) content, dihydropyrimidine dehydrogenase (DPD) activity, the TS inhibition rate (TS-IR), and 5-FU incorporated into RNA (F-RNA) in four human gastric cancer xenografts (MKN-28, MKN-74, GCIY and GT3TKB) and compared the results obtained with S-1 with those obtained with 5-FU and UFT (1 M tegafur, 4 M uracil). 5-FU was administered intraperitoneally (i.p.) to mice at a dose of 50 mg/kg, three times, on days 0, 4 and 8. S-1 and UFT were administered orally at doses of 10 and 24 mg/kg, respectively, once a day, for 9 consecutive days. Antitumour activity was evaluated as the maximum inhibition of tumour growth in each animal. S-1 showed a better antitumour activity than 5-FU and UFT in tumours with a high DPD activity (GCIY and GT3TKB). There were inverse correlations between the antitumour activity and both TS content and DPD activity in the 5-FU and UFT groups. However, no such correlations were observed in the S-1 group. In GCIY and GT3TKB xenografts, TS-IR was significantly higher in the S-1 group than in the 5-FU or UFT groups. In GT3TKB xenografts, the F-RNA level was significantly higher in the S-1 group than in the 5-FU or UFT groups. The superior cytotoxicity of S-1 appears to be attributable to both an increased inhibition of DNA synthesis and an enhanced blockade of RNA function against tumours with a high DPD activity.

Answer 44:

Bibliographic Information

Prediction of sensitivity to fluoropyrimidines by metabolic and target enzyme activities in gastric cancer. Terashima Masanori; Fujiwara Hisataka; Takagane Akinori; Abe Kaoru; Irinoda Takashi; Nakaya Tsutomu; Yonezawa Hitoshi; Oyama Kenichi; Saito Kazuyoshi; Kanzaki Norio; Ohtani Satoshi; Nemoto Tsuyoshi; Hoshino Yutaka; Kogure Michihiko; Gotoh Mitsukazu First Department of Surgery, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association (2003), 6 Suppl 1 71-81. Journal code: 100886238. ISSN:1436-3291. (CLINICAL TRIAL); (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 12775024 AN

2003251023 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: This study was designed to investigate the role of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and thymidine phosphorylase (TP) in tumor progression and sensitivity to 5-fluorouracil (5-FU). METHODS: A total of 275 tumor samples from 275 patients with gastric cancer were utilized in this study. TS activity was determined in 130 samples by 5-fluorodeoxyuridine monophosphate binding assay. DPD activity was measured in 140 samples by radioenzymatic assay, and TP protein level was determined in 157 samples by an enzyme-linked immunosorbent assay (ELISA) system. These parameters were compared with several clinicopathologic factors and sensitivity to 5-FU determined by in-vitro ATP assay. The antitumor activities of 5-FU, uracil plus tegafur (UFT), and 1M tegafur--0.4 M 5-chloro-2,4-dihydroxypyridine--1 M potassium oxonate (S-1 [TS-1]) were also compared, using three human gastric cancer xenografts in nude mice. RESULTS: There was no correlation between either TS or TP and sensitivity to 5-FU. However, a weak inverse correlation was found between DPD activity and sensitivity to 5-FU. High DPD activity in tumor resulted in poor prognosis, especially in patients who received 5-FU-based adjuvant chemotherapy. Although TP was significantly correlated with depth of tumor invasion and with lymphatic and venous invasions, TP alone had no impact on survival. On the other hand, TS, as well as peritoneal, hepatic, and lymph node metastases, was selected as an independent prognostic factor in gastric cancer. In the animal model, there was no significant difference in antitumor activities among the drugs in a tumor with low DPD activity. However, S-1 showed superior antitumor activity to 5-FU or UFT in tumors with high DPD activity. CONCLUSION: DPD is considered to be a most important predictive factor of 5-FU sensitivity. The use of DPD inhibitory fluoropyrimidines is strongly recommended for tumors with high DPD activity.

Answer 45:

Bibliographic Information

Chemosensitivity of peritoneal micrometastases as evaluated using a green fluorescence protein (GFP)-tagged human gastric cancer cell line. Nakanishi Hayao; Mochizuki Yoshinari; Kodera Yasuhiro; Ito Seiji; Yamamura Yoshitaka; Ito Katsuki; Akiyama Seiji; Nakao Akimasa; Tatematsu Masae Division of Oncological Pathology, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681. hnakanis@aichi-cc.jp Cancer science (2003), 94(1), 112-8. Journal code: 101168776. ISSN:1347-9032. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 12708484 AN 2003189190 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The chemosensitivity of micrometastases in the peritoneal cavity to a 5-fluorouracil derivative (TS-1) was examined with a micrometastasis model featuring a human gastric cancer cell line tagged with the green fluorescence protein (GFP) gene in nude mice. Peritoneal metastases on the omentum and mesentery could be specifically visualized even when minute or dormant and also externally monitored noninvasively under illumination with blue light from 1 day after intraperitoneal (i.p.) injection of tumor cells. Metastatic deposits formed after i.p. injection of 2x10(6) tumor cells were significantly reduced by TS-1 in a dose-dependent manner (15-20 mg/kg), when it was orally administered from day 1 post-injection for 4 weeks (early administration). No such inhibition was evident after injection of 1x10(7) tumor cells. When 2x10(6) tumor cells given injection, the ascites-free period in TS-1-treated mice was significantly longer than in their untreated counterparts. Survival of TS-1-treated mice (5/15) was also significantly higher than the zero rate in controls (0/15), with 4 out of 5 surviving mice being free from peritoneal metastasis and the exception having only a few dormant metastases. In contrast, when TS-1 was administered starting from day 7 post-injection for 4 weeks (late administration), the survival and ascites-free period of the TS-1-treated mice were not significantly influenced. The results indicate that the chemosensitivity of peritoneal metastases to TS-1 is dependent on the number of i.p. tumor cells and the timing of drug administration. Peritoneal micrometastases at an early stage are most susceptible and can be effectively eliminated by oral administration of an anti-cancer agent, which leads to the longer survival and better quality of life (QOL) of the mice.

Answer 46:

Bibliographic Information

A potential important role for thymidylate synthetase inhibition on antitumor activity of fluoropyrimidine and raltitexed. Kabeshima Yasuo; Kubota Tetsuro; Watanabe Masahiko; Saikawa Yoshiro; Nishibori Hideki; Hasegawa Hirotoshi; Kitajima Masaki Department of Surgery, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan Anticancer research (2002), 22(6A), 3245-52. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 12530071 AN 2003024084 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Because thymidylate synthetase (TS) is a key enzyme in DNA synthesis, it has been used as a target for cancer chemotherapy. MATERIALS AND METHODS: We investigated the combined antitumor activity of raltitexed, 5-FU and UFT on human tumor xenografts in nude mice and examined changes in TS activity and 5-FU-bound RNA (F-RNA) levels. Human gastric (SC-1-NU) or colon (HT-29) carcinoma xenografts were transplanted subcutaneously into nude mice, and drugs administered intraperitoneally (raltitexed and 5-FU) or perorally (UFT) daily for 5 days, and repeated once after a 2-day interval. RESULTS: The antitumor effects were mostly equivalent between the treatment groups despite the different drugs and sequence orders. TS inhibition rates correlated with the tumor inhibition rate, which was statistically significant, while F-RNA levels did not correlate with antitumor activity. CONCLUSION: Our results indicated that the combination of fluoropyrimidine-related agents should be directed towards increased TS inhibition rather than increased F-RNA levels.

Answer 47:

Bibliographic Information

gamma-Hydroxybutyric acid and 5-fluorouracil, metabolites of UFT, inhibit the angiogenesis induced by vascular endothelial growth factor. Basaki Y; Chikahisa L; Aoyagi K; Miyadera K; Yonekura K; Hashimoto A; Okabe S; Wierzba K; Yamada Y Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd, Hanno City, Saitama, Japan. y-basaki@taiho.co.jp Angiogenesis (2001), 4(3), 163-73. Journal code: 9814575. ISSN:0969-6970. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11911014 AN 2002178982 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

UFT, a drug composed of uracil and tegafur at the molar ratio of 4:1, is an orally active agent for the treatment of a wide variety of malignant tumours. Using a murine dorsal air sac (DAS) assay, we have previously shown that UFT and its metabolites, gamma-hydroxybutyric acid (GHB) and 5-fluorouracil (5-FU), inhibited the angiogenesis induced by murine renal cell carcinoma. Here we report that UFT was more effective than other fluorinated pyrimidines such as 5-FU and doxifluridine (5'-DFUR) in blocking the angiogenic responses elicited by five human cancer cell lines which produced high levels of vascular endothelial growth factor (VEGF), but no detectable fibroblast growth factor-2 (FGF-2) in vitro. In contrast, UFT was unable to block the angiogenic response to one human gastric cancer cell line which produced both VEGF and FGF-2 in vitro. However, the production or secretion of VEGF by these cells was unaffected by GHB and 5-FU treatment. Interestingly, GHB suppressed the chemotactic migration and tube formation of human umbilical vein endothelial cells (HUVECs) stimulated by VEGF, without inhibiting their DNA synthesis. Since GHB did not affect the FGF-2-driven activities in HUVECs, its action appears to be VEGF-selective. On the other hand, 5-FU inhibited DNA synthesis and migration of HUVECs stimulated by both VEGF and FGF-2, and tube formation driven by VEGF, suggesting that 5-FU is cytotoxic to endothelial cells. The inhibitory effects of 5-FU, and especially those GHB, were reproduced under in vivo condition using the DAS assay. The VEGF-mediated angiogenesis was significantly inhibited by UFT, 5-FU, and especially by GHB. We propose that the selective inhibitory effects of GHB on VEGF-mediated responses of endothelial cells are involved in the anti-angiogenic activity of UFT.

Answer 48:

Bibliographic Information

Gamma-hydroxybutyric acid, a metabolite of UFT, shows anti-angiogenic activities and antitumor effect. Basaki Yuji; Miyadera Kazutaka; Yonekura Kazuhiko; Aoyagi Kumio; Chikahisa Lumi; Okabe Soko; Hashimoto Akihiro; Kitazato Kenji Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd Gan to kagaku ryoho. Cancer & chemotherapy (2002), 29(1), 89-94. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 11816484 AN 2002089666 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We investigated the antitumor vasculogenesis and antitumor activity of gamma-hydroxybutyric acid (GHB), a metabolite of UFT. In a mouse dorsal air sac (DAS) assay, UFT demonstrated a wide spectrum of anti-tumor vasculogenesis except for AZ-521 tumor. Although the expression of vascular endothelial growth factor (VEGF) was detected in almost all tumor cell lines used in the DAS assays, expression of basic fibroblast growth factor (bFGF) was only detected in the AZ-521 tumor. GHB inhibited the chemotactic migration and morphological changes of human umbilical vein endothelial cells (HUVECs) induced by VEGF at IC50 values of 2.8 and 0.31 microM respectively. In addition to these in vitro assays, GHB blocked tumor growth of MC-5, a human breast cancer, in a xenograft model at inhibition rate of 37%. Moreover, GHB showed an additive effect in combination with 5-FU in this model. These results indicate that the anti-tumor vasculogenesis activity of GHB is involved in part in the antitumor effect of UFT.

Answer 49:

Bibliographic Information

Suppression of mediastinal metastasis by uracil-tegafur or cis-diamminedichloroplatinum(II) using a lymphogenous metastatic model in a human lung cancer cell line. Ishikura H; Kondo K; Miyoshi T; Kinoshita H; Takahashi Y; Fujino H; Monden Y Second Department of Surgery, School of Medicine, University of Tokushima, 3-18-15 Kuramoto-cho, Tokushima City, Tokushima 770-8503, Japan Clinical cancer research : an official journal of the American Association for Cancer Research (2001), 7(12), 4202-8. Journal code: 9502500. ISSN:1078-0432. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11751521 AN 2002002468 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE AND EXPERIMENTAL DESIGN: The extent of lymphatic metastasis is the most important factor in the prognosis for non-small cell lung cancer (NSCLC). Therefore, suppression of lymphatic metastasis provides an improvement in survival time in lung cancer patients. We established a new patient-like model for lung cancer metastasis by orthotopic implantation in severe combined immunodeficiency (SCID) mice and demonstrated the lymphogenous spread histologically using human NSCLC cell lines. The cardinal features of this model are a simple procedure and a similarity to the metastatic form of human lung cancer. The purpose of this study is to assess the inhibitory action of uracil-tegafur (UFT) and cis-diamminedichloroplatinum(II) (CDDP) on lymphatic metastasis and life span prolongation in our lymphogenous metastatic model system using SCID mice. RESULTS: The inhibition ratios of mediastinal lymph node metastasis were 86.2, 94, and 92.1% for 12 mg/kg body UFT, 17 mg/kg body UFT, and 10 mg/kg body CDDP, respectively. The administration of anticancer drugs prolonged the life span by 4.6 days (17 mg/kg body UFT) and 8 days (10 mg/kg body CDDP) in MST. CONCLUSION: We demonstrated that UFT alone and CDDP alone suppressed mediastinal metastasis and prolonged the life span in our lymphogenous metastatic model. Regardless of the administration route and characteristics of anticancer drugs, cytostatic or cytotoxic, our model is capable of evaluating the inhibitory effect of drugs on lymphatic metastasis. This model should make an important contribution to our understanding of the mechanism and selection of drugs for antilymphatic metastasis in lung cancer.

Answer 50:

Bibliographic Information

Animal model of para-aortic lymph node metastasis. Tsutsumi S; Kuwano H; Morinaga N; Shimura T; Asao T First Department of Surgery, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi 371-8511, Japan. chuchumi@showa.gunma-u.ac.jp Cancer letters (2001), 169(1), 77-85. Journal code: 7600053. ISSN:0304-3835. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11410328 AN 2001347195 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The purpose of this study was to establish a model of experimental lymph node metastasis by intra-rectal implantation of human cancer cells in nude mice. Four types of human cancer cell lines (TE-1, MKN-45, HT-29, and MIAPaca-2) were investigated. Tumor cells suspended in Matrigel were injected into the submucosal layer of the rectum. All cancer cell lines produced locally aggressive rectal tumors and, subsequently, para-aortic lymph node metastasis. We were unable to produce other distant metastases in the dying state in such locations as the liver, spleen, lung, and peritoneum. However, using this method, we were able to evaluate the effect of the anti-cancer agent uracil/tegafur (UFT) on primary tumor growth and lymph node metastasis. Oral intake of UFT significantly suppressed implanted tumor volume and inhibited lymph node metastasis. We expect that the process of lymph node metastasis shown in this model will be studied as an experimental model of lymph node metastasis simulating human cancers.

Answer 51:

Bibliographic Information

An experimental model of tumor dormancy therapy for advanced head and neck carcinoma. Nishimura G; Yanoma S; Satake K; Ikeda Y; Taguchi T; Nakamura Y; Hirose F; Tsukuda M Department of Otorhinolaryngology, Yokohama City University School of Medicine, Kanazawa-ku, Yokohama 236-0004, Japan. go_c@med.yokohama-cu.ac.jp Japanese journal of cancer research : Gann (2000), 91(11), 1199-203. Journal code: 8509412. ISSN:0910-5050. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11092987 AN 2001101555 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

An experimental model of tumor dormancy therapy for advanced head and neck carcinoma was developed. After transplantation of KB cells into nude mice, the mice were given tiracoxib, a selective cyclooxygenase (COX)-2 inhibitor, probucol, an antioxidant, and S-1, an oral pro-drug of 5-fluorouracil (5-FU), or combinations of two of them. The combined administration of tiracoxib with probucol significantly inhibited the tumor growth. The angiogenesis in this group was markedly reduced. Tiracoxib and probucol did not affect the intratumoral concentration of 5-FU when coadministered with S-1. The combined use of tiracoxib and probucol is thus a candidate for use in maintenance therapy after the primary therapy for patients with advanced head and neck carcinoma.

Answer 52:

Bibliographic Information

Therapeutic effect of 1 M tegafur-0.4 M 5-chloro-2, 4-dihydroxypridine-1 M potassium oxonate (S-1) on head and neck squamous carcinoma cells. Nishimura G; Yanoma S; Mizuno H; Satake K; Taguchi T; Ikeda Y; Tsukuda M Department of Otorhinolaryngology, Yokohama City University, School of Medicine, 3-9 Fukuura, Kanazawa-ku, 236-0004, Yokohama, Japan. go_c@med.yokohama-cu.ac.jp Cancer letters (2000), 159(1), 1-7. Journal code: 7600053. ISSN:0304-3835. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT,

NON-U.S. GOV'T) written in English. PubMed ID 10974399 AN 2001013978 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

1 M Tegafur (FT)-0.4 M 5-chloro-2,4-dihydroxypridine (CHDP)-1 M potassium oxonate (Oxo) (S-1), was developed as a new oral antineoplastic agent based on biochemical modulation of fluorouracil (5-FU) by CHDP and Oxo. The antitumor effect of S-1 on human head and neck squamous carcinoma cells was evaluated in xenografts and a metastasis model, in comparison with combined drug of 1 M FT and 4 M uracil (UFT). Mice treatment with S-1 showed a significant higher concentration of 5-FU in the tumor and the serum than UFT treated mice. S-1 showed higher tumor growth inhibition and metastasis inhibition than UFT. The mice in which metastasis was inhibited lived more than twice as long as the control mice. These results suggest that S-1 will have a higher clinical therapeutic effect against advanced squamous cell carcinoma of the head and neck in humans.

Answer 53:

Bibliographic Information

Antitumor activity of UFT and docetaxel on human breast carcinoma xenografts. Yamada T; Yamada Y; Asanuma F; Kawamura E; Suzuki T Biomedical Laboratory, Kitasato Institute Hospital Gan to kagaku ryoho. Cancer & chemotherapy (2000), 27(11), 1725-30. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 11057324 AN 2000507053 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The effect of fluorinated pyrimidine co-administered with docetaxel on transplantable human breast cancer strains MX-1 and R-27 was investigated using an in vitro succinic dehydrogenase inhibition (SDI) method and an in vivo nude mouse transplant method. The in vivo results showed that the combined use of 5-fluorouracil and docetaxel enhanced antitumor activity. No antitumor activity on MX-1 was observed in vivo in either the UFT alone or docetaxel alone group, whereas co-administration of the two drugs resulted in a tumor inhibition rate of 85.1% above the effective line. These results suggest the usefulness of 5-fluorouracil in combination with docetaxel in the treatment of solid tumors.

Answer 54:

Bibliographic Information

Synergistic antitumoral activity of combined UFT, folinic acid and oxaliplatin against human colorectal HT29 cell xenografts in athymic nude mice. Louvet C; Coudray A M; Tournigand C; Prevost S; Raymond E; de Gramont A; Chazard M; Gespach C INSERM Unit 482, Hopital St-Antoine, Paris, France. christophe.louvet@sat.ap-hop-paris.fr Anti-cancer drugs (2000), 11(7), 579-82. Journal code: 9100823. ISSN:0959-4973. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11036962 AN 2000486514 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

This study was designed to assess the inhibition of tumor growth by oxaliplatin combined with UFT and folinic acid (FA). Growth inhibition was studied in nude mice transplanted with human colorectal HT29 tumor cell xenografts and treated for 28 days with oral UFT (20 mg/kg/day) and FA (4 mg/kg/day), i.p. oxaliplatin (10 mg/kg on day 1) or a combination of oxaliplatin, UFT and FA, or else not treated (controls). Tumor surface area and weight were recorded twice a week, and mice were sacrificed at day 28. Two separate experiments were performed for each group of 25 mice. At day 28, mean

tumor weights (g) were 2.89+/-0.22 (controls), 2.03+/-0.14 (oxaliplatin), 2.02+/-0.21 (UFT/FA) and 1.23+/-0.17 (oxaliplatin+UFT/FA). For the three treatment groups, tumor weight decreases were 30.1% ($p<0.05$), 29.9% ($p<0.05$) and 57.5% ($p<0.001$), respectively. Combined treatment (UFT/FA+oxaliplatin) reduced tumor weight by 39% compared to oxaliplatin alone ($p<0.05$) or UFT/FA ($p<0.05$). These results demonstrate the synergistic effect of the combination of oxaliplatin, UFT and FA in this HT29 cell xenograft model, and warrant further investigations in patients with metastatic colorectal cancer.

Answer 55:

Bibliographic Information

Antitumor efficacy of combination chemotherapy with UFT and cyclophosphamide against human breast cancer xenografts in nude mice. Haga S; Shimizu T; Imamura H; Watanabe O; Kinoshita J; Fukushima M; Kajiwara T Department of Surgery, Tokyo Women's Medical College Daini Hospital, Japan Anticancer research (1999), 19(3A), 1791-6. Journal code: 8102988. ISSN:0250-7005. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10470117 AN 1999399103 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The combination of cyclophosphamide (CPA) and 5-fluorouracil (5-FU) is currently regarded as the most effective therapy for the treatment of patients with advanced and recurrent breast cancer. We evaluated the augmentation of antitumor activity and toxicity by coadministration of CPA and UFT (1M tegafur--4M uracil) instead of intravenous 5-FU on H-31 human breast cancer xenografts in nude mice. The maximum tolerable dose (MTD) of UFT alone (24 mg/kg) and CPA alone (85 mg/kg) had a significant effect on H-31 tumors in mice with 86.6% and 83.0% inhibition rates of tumor growth, respectively, and without loss of body weight, diarrhea or myelosuppression. The combined administration with full and 83.3% MTD of UFT and CPA augmented the antitumor activity compared to that of UFT alone and CPA alone. The relative tumor volume of the UFT plus CPA-treated group to the UFT- and CPA-treated groups was 0.28 and 0.36 for the full MTD, and 0.51 and 0.67 for 83.3% MTD, respectively. When CPA was consecutively administered to the tumor-bearing mice for 14 days, there were no decreases in the activities of enzymes related to 5-FU metabolism, but there was an significant increase in the activity of ribonucleotide reductase, suggesting that anabolism of 5-FU derived from tegafur is accelerated to some extent by coadministration of CPA. In conclusion, these results suggest that combination therapy with oral UFT and CPA may be useful for the long-term treatment of cancer patients with advanced and recurrent breast cancers.

Answer 56:

Bibliographic Information

Therapeutic effect of 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) on liver metastasis of xenotransplanted human colon carcinoma. Konno H; Tanaka T; Baba M; Kanai T; Matsumoto K; Kamiya K; Nakamura S Department of Surgery II, Hamamatsu University School of Medicine. hkonno@hama-med.ac.jp Japanese journal of cancer research : Gann (1999), 90(4), 448-53. Journal code: 8509412. ISSN:0910-5050. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10363584 AN 1999290252 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

S-1 [1 M tegafur (FT)-0.4 M 5-chloro-2,4-dihydroxypyridine (CDHP)-1 M potassium oxonate (Oxo)], was developed as a new oral antineoplastic agent based on biochemical modulation of fluorouracil (5-FU) by CDHP and Oxo. The therapeutic effect of S-1 on human colon cancer xenografts (TK-13) with high metastatic potential to the liver was evaluated. Small pieces of TK-13 were sutured into the cecal wall of 52 nude mice, and the animals were randomly divided into 3 groups

[control (n=17), UFT (combination of 1 M FT and 4 M uracil) (n=18) and S-1 (n=17)]. S-1 or UFT was administered orally at an equitoxic dose (S-1, 7.5 mg/kg; UFT, 17.5 mg/kg as FT) for 37 consecutive days beginning 10 days after the transplantation. S-1 showed higher tumor growth inhibition than UFT (P<0.05) and also showed a significant anti-metastatic effect on liver metastasis, while UFT did not. Liver metastasis developed in only 2 of the 17 mice (12%) in the S-1 group, whereas it developed in 9 of the 17 (53%) and 7 of the 18 (39%) in the control and UFT group, respectively. Analysis of AUC (area under the curve) revealed that S-1 yielded higher 5-FU levels in both tumor tissue (1.6 times) and plasma (2.5 times) than UFT. These results suggest that S-1 will show a higher clinical therapeutic effect against human colorectal cancer than UFT.

Answer 57:

Bibliographic Information

Postsurgical oral administration of uracil and tegafur inhibits progression of micrometastasis of human breast cancer cells in nude mice. Kurebayashi J; Nukatsuka M; Fujioka A; Saito H; Takeda S; Unemi N; Fukumori H; Kurosumi M; Sonoo H; Dickson R B Department of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-01, Japan Clinical cancer research : an official journal of the American Association for Cancer Research (1997), 3(5), 653-9. Journal code: 9502500. ISSN:1078-0432. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 9815733 AN 1999110982 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We recently established a metastasis model in nude mice using the MKL-4 cell line, a contransfectant of the MCF-7 human breast cancer cell line with fgf-4 and lacZ in which micrometastases in several organs can be quantitatively observed. First, to develop a new postsurgical metastasis model, we investigated the timing of occurrence of micrometastasis and the influence of tumor removal on the progression of micrometastasis in this model. Micrometastases into lymph nodes and lungs were detected 3 weeks after the cell injections. Tumor removal 3 weeks after the injections significantly enhanced the progression of micrometastasis into lymph nodes and bone. Second, to study the effect of a mixed compound, UFT (a molar ratio of uracil:tegafur of 4:1), which has been widely used in the postsurgical adjuvant setting in Japan, 15 or 20 mg/kg UFT were administered p.o. for 4 weeks to tumor-bearing mice or to mice in which transplanted tumors were resected 3 weeks after the injections. Either dose of UFT significantly inhibited the tumor growth as well as the progression of micrometastasis into lymph nodes, lungs, liver, and brain. In addition, enhanced progression of micrometastasis in all explored organs by the tumor removal was significantly inhibited by the administration of either dose of UFT. In conclusion, this new postsurgical metastasis model may be useful for evaluating the efficacy of agents used in the postoperative adjuvant setting. UFT may be an effective drug for inhibiting the progression of micrometastasis after surgery.

Answer 58:

Bibliographic Information

Preclinical antitumor efficacy of S-1: a new oral formulation of 5-fluorouracil on human tumor xenografts. Fukushima M; Satake H; Uchida J; Shimamoto Y; Kato T; Takechi T; Okabe H; Fujioka A; Nakano K; Ohshimo H; Takeda S; Shirasaka T Cancer Research Laboratory-2, Hanno-City, Saitama 357, Japan International journal of oncology (1998), 13(4), 693-8. Journal code: 9306042. ISSN:1019-6439. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9735397 AN 1998408006 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

S-1 is a new oral formulation of 5-fluorouracil (5-FU) consisted of 1M tegafur, 0.4M 5-chloro-2,4-dihydroxypyridine that inhibits a degradation of 5-FU, and 1M potassium oxonate that regulates the phosphorylation of 5-FU in the gastrointestinal tract, and has shown excellent antitumor efficacy against various murine tumors in rodents, compared to the oral tegafur-based antitumor drug, UFT (1M tegafur plus 4M uracil), which is used clinically in Japan. To assess the possibility of clinically using S-1, we investigated the antitumor effect of S-1 on various human solid tumor xenografts in athymic rats and mice. In the nude rat system, S-1 was significantly effective against all 12 tumor xenografts tested when its minimum toxic dose (15 mg/kg) was administered for 14 days. Three tumors, stomach (H-81), colon (KM12C) and breast (H-31) markedly regressed in response to treatment with S-1 but not with UFT. The antitumor potency of S-1 was weak against human tumors xenografted into nude mice and likely similar to that of UFT. The reason of the discrepancy in the efficacy of S-1 between rats and mice was found to be that the 5-FU levels in the blood and tumor tissue of rats after oral administration of S-1 persisted much longer than in mice, and this prolonged maintenance of plasma 5-FU levels was significantly related to the potent antitumor activity of S-1. In conclusion, the results of this study suggested that based on its biological and pharmacokinetic characteristics, oral S-1 should be active against various human cancers.

Answer 59:

Bibliographic Information

Invention of a tumor-selective 5-fluorouracil derivative named S-1 by biochemical modulation of 5-fluorouracil. Shirasaka T; Shimamoto Y; Kato T; Fukushima M Institute for Pathogenic Biochemistry in Medicine Gan to kagaku ryoho. Cancer & chemotherapy (1998), 25(3), 371-84. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in Japanese. PubMed ID 9492831 AN 1998153830 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A new oral type of 5-fluorouracil (5-FU) derivative possessed of both potent antitumor activity and less gastrointestinal (GI) toxicity was investigated and developed in the form of a combination of tegafur (FT), a masked form of 5-FU, and its two peculiar biochemical modulators. One is 5-chloro-2,4-dihydroxypyridine (CDHP), a new potent inhibitor of 5-FU degradation in vivo, and another is potassium oxonate (Oxo), a characteristic inhibitor of 5-FU phosphorylation, which distributes much higher in GI tract after p.o. administration. 5-FU levels in blood of rats following administration of FT, were markedly elevated and persisted for a long-time by co-oral CDHP corresponding to over 0.4 molar ratio to FT, like the case in continuous infusion of 5-FU, which resulted in an augmentation of antitumor efficacy in Yoshida sarcoma-bearing rats, although severe GI toxicity simultaneously occurred. To reduce 5-FU-induced toxicities such as diarrhea and body weight loss and to maintain the augmented antitumor activity, 0.5 to 2 molar Oxo was orally given to rats with one molar FT plus 0.4 molar CDHP. As a result, both severe GI injury and body weight loss were markedly inhibited by coadministration of 0.5 to 1.0 molar Oxo while high antitumor efficacy (about 90% inhibition of tumor growth) was maintained. However, such almost complete antitumor effect was reduced to about 50% inhibition of tumor growth by over 2 molar Oxo combined with one molar FT plus 0.4 molar CDHP. Based on these results, a novel 5-FU derivative, named S-1, was composed of one molar FT, 0.4 molar CDHP and one molar Oxo. S-1 showed an antitumor activity over 3-fold stronger than UFT (one molar FT plus 4 molar uracil) against Yoshida sarcoma and Sato lung carcinoma in rats and human colon carcinoma (KM12C) xenografted in nude rats when its minimum toxic dose was administered. Co-oral Oxo also significantly reduced the incidence of diarrhea and stomatitis induced by administration of FT-CDHP in beagle dogs.

These results suggest that high antitumor activity and less GI toxicity of S-1 was brought about by the elevation in blood and tumor tissues and by selective decrease of 5-fluoronucleotides, an active metabolite of 5-FU, in GI tract.

Answer 60:

Bibliographic Information

Augmentation of the chemotherapeutic effectiveness of UFT, a combination of tegafur

[1-(2-tetrahydrofuryl)-5-fluorouracil] with uracil, by oral l-leucovorin. Okabe H; Toko T; Saito H; Nakano K; Fujioka A; Yuasa C; Takeda S; Unemi N Anticancer and Antimicrobials Research Lab, Taiho Pharmaceutical Co., Ltd, Tokushima, Japan Anticancer research (1997), 17(1A), 157-64. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9066646 AN 97219346 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

UFT, combination of tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] with uracil, is widely-used as an anti-neoplastic agent in Japan. We evaluated the anti-tumor efficacy of the combined modality of UFT with oral l-leucovorin. The augmentation of anti-tumor activity of UFT by co-administration of l-leucovorin was observed over a dose of 1.85 mg/kg (5.55 mg/m2) and was significant at a dose of 5.56 mg/kg (16.7 mg/m2). Using ten human tumor xenografts, l-leucovorin significantly enhanced the growth-suppressive ability of UFT against colon carcinoma (KM20C, Col-1) and mammary carcinoma (H-31, MX-1). Among various 5-fluorouracil (FUra) derivatives, such as UFT, 5'-deoxy-5-fluorouridine (5'-DFUR) and FUra, l-leucovorin gave the maximum augmentation to the anti-tumor activity of UFT, due to the prolonged half-life of FUra in plasma. Enhancement of the cytotoxic activity of FUra by l-leucovorin against KM20C colon carcinoma cell line was observed in a time-dependent manner at a concentration of 0.01 microM l-leucovorin. Based on these results, we conclude that the combination of UFT with oral l-leucovorin has significant antitumor activity and represents an interesting regimen to be evaluated in the clinical setting.

Answer 61:

Bibliographic Information

The modulating effect of interferon alpha-2a on the antitumor activity of UFT against a human gastric carcinoma xenograft, SC-1-NU, in nude mice. Kubota T; Kurihara N; Kase S; Watanabe M; Kumai K; Kitajima M; Inada T Department of Surgery, School of Medicine, Keio University, Tokyo, Japan Surgery today (1996), 26(1), 12-4. Journal code: 9204360. ISSN:0941-1291. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8680114 AN 96272739 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The modulating effect of recombinant human interferon alpha-2a (IFN) on the antitumor activity of UFT, a mixed compound of tegafur and uracil at a molar ratio of 1:4, was investigated against SC-1-NU, a human gastric cancer xenograft serially transplanted in nude mice. IFN was administered subcutaneously at a dose of 60,000 IU/mouse daily for 14 days, and UFT was given at a dose of 15 mg/kg as tegafur daily, except on Sundays, for 3 weeks. The agents were administered either alone or simultaneously. Synergistic antitumor activity on SC-1-NU was produced by the combination of IFN and UFT without any increment of side effects, and the combination therapy also increased intratumoral thymidylate synthetase (TS) inhibition and the amount of 5-fluorouracil (5-FU) in the intratumoral RNA. Thus, IFN seems to modulate the antitumor activity of UFT against SC-1-NU through an inhibition of DNA synthesis and RNA distortion, and therefore this combination could be useful for clinical application.

Answer 62:

Bibliographic Information

Augmentation of chemotherapeutic efficaciousness of UFT by oral l-leucovorin--growth-inhibitory activity of combination against human tumor xenograft. Saito H; Okabe H; Nakano K; Fujioka A; Toko T; Takeda S; Unemi N Anticancer and Antimicrobials Research Lab., Taiho Pharmaceutical Co., Ltd Gan to kagaku ryoho. Cancer & chemotherapy (1995), 22(13), 1919-25. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 7487121 AN 96083692 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Combination chemotherapy with FUra and LV has been reported as a useful treatment for patients suffering from colon carcinoma. Usually, both FUra and LV are administered by intravenous infusion, but not orally. UFT, an anti-neoplastic agent consisting of FT and uracil, is widely used for oral administration in Japan. Using human tumor xenografts of 10 cell lines, we evaluated the efficacy of UFT combined with l-LV, which is the active form of LV, by oral administration. Combined treatment of UFT with l-LV was more effective than UFT alone on the growth suppression of colon carcinoma (KM 20 C, Col-1) and mammary carcinoma (H-31, MX-1). When 1.85 mg/kg (5.55 mg/m2) of LV was given to tumor bearing mice, the antitumor activity of UFT was augmented and at a dose of 5.56 mg/kg (16.7 mg/m2) of LV, it was significantly augmented. Among various 5-FU derivatives, such as UFT, 5'-DFUR or FUra, combined treatment using UFT with l-LV was the most effective by oral administration. l-LV did not improve the anti-tumor efficacy or toxicity of 5'-DFUR. l-LV seemed to augment the anti-tumor activity of FUra, but not significantly. These results suggest that combination chemotherapy of UFT with LV is a promising approach for the clinical treatment of human colon cancer.

Answer 63:

Bibliographic Information

Light and electron microscopic examination compared to evaluation by tumor size in subrenal capsule assay for chemosensitivity testing in esophageal cancer. Akao S; Oya M; Ishikawa H; Kiumi F Dept. of Surgery, Koshigaya Hospital, Dokkyo University School of Medicine Gan to kagaku ryoho. Cancer & chemotherapy (1995), 22(12), 1813-9. Journal code: 7810034. ISSN:0385-0684. (COMPARATIVE STUDY); (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 7574815 AN 96028148 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Specimens from six clinical cases of esophageal cancer were transplanted under the renal capsule of AF nude mice, and chemosensitivity to anticancer drugs (UFT, CDDP) was evaluated by measuring tumor size (SRC). Histological analysis of the xenografts by light (LM) and electron microscopy (EM) was also performed to confirm the precision of this original method used for SRC. Two-dimensional morphometry by EM was also performed in four cases. With the exception of one case, the same results were obtained by graft measurement analysis and light microscopic observation, which allowed easy evaluation by observing cancer pearl formation, prominent proliferation of tumor cells or total cell keratinization. However, there was no false-positive sensitivity in the former method. EM observation did not reveal any special findings with regard to chemotherapy response, but increased numbers of cytoplasmic vacuoles and desmosomes, cytoplasmic swelling, a reduction of the N/C ratio and nuclear deformity implied common changes to cell necrosis induced by the anticancer drugs. For clinical use of SRC against esophageal cancer, it is supposed to be best to compare LM histological evaluation, which is too complicated and time consuming. For this reason, it is potentially useful to perform SRC by evaluating tumor size, because another goal of chemosensitivity testing involves determination of anticancer drugs without effectiveness.

Answer 64:

Bibliographic Information

Effect of UFT and CBDCA combined therapy on human laryngeal cancer transplanted into nude mice. Kubota T; Nishimura T Dept. of Otorhinolaryngology, Fujigaoka Hospital, Showa University Gan to kagaku ryoho. Cancer & chemotherapy (1993), 20(13), 1961-5. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 8215469 AN 94029039 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Nude mice transplanted with a human tumor of the larynx were treated by combination therapy with UFT and carboplatin (CBDCA) for a prolonged period (3 months). To compare the combination therapy with UFT or CBDCA treatment alone, the mice were divided into four groups; control group, group orally given UFT (20mg/kg, five times a week for 3 months), group intraperitoneally given ip CBDCA (50mg/kg, every 3 weeks for 3 months), and group given combination therapy with UFT and CBDCA. No antitumor effect was observed in the group received UFT or CBDCA alone, while a significant antitumor effect was noted in the combination therapy group, compared to the control as evidenced by DNA histogram, showing a decrease in atypical cell count. The results of this study suggest that the combination of UFT and CBDCA provides an efficacious chemotherapy for cancers of the head and neck.

Answer 65:

Bibliographic Information

Antitumor activity of BOF-A2, a new 5-fluorouracil derivative, against human cancers xenografted in nude mice by intermittent administration. Fujita F; Fujita M; Inaba H; Taguchi T Dept. of Surgery, Osaka University, Suita, Japan Gan to kagaku ryoho. Cancer & chemotherapy (1993), 20(2), 223-8. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 8434959 AN 93167874 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Antitumor effects of BOF-A2 given intermittently was evaluated with human gastric (H-111, H-83), colorectal (H-110, H-143) and lung (H-74, LC-376) cancers xenografted in nude mice and compared with those by continuous administration. BOF-A2 was orally given 3 or 4 times per week at 30 or 35 mg/kg over 4 weeks. This drug was effective to 5 strains except H-110 (IR > or = 58%), remarkably effective to H-81 and H-143 (IR > or = 80%) and caused tumor regression in mice bearing H-81 especially. Moreover, the drug was effective to H-74 which is rather insensitive to 5-FU and its known derivatives. When the drug was given orally to nude mice xenografted LC-376, 5-FU levels in the tumor tissue was notably durative for a long time as compared to UFT. It would be concluded that BOF-A2 was much effective to insensitive tumor to fluorinated pyrimidines or other anticancer, because of persistence of high levels of 5-FU in the tumor tissue. On the other hand, diarrhea which is caused by other fluorinated pyrimidines or consecutive administration of BOF-A2, was mild by the intermittent administration of BOF-A2.

Answer 66:

Bibliographic Information

Electron microscopic study on the method of evaluation of SRC assay. Akao S; Iwami N; Ishikawa H; Kiumi F Dept. of Surgery, Koshigaya Hospital, Dokkyo University, School of Medicine, Koshigaya, Japan Gan to kagaku ryoho. Cancer & chemotherapy (1992), 19(11), 1817-23. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 1519924 AN 92391866 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The subrenal capsule assay (SRC) is a rapid and precise method for evaluation of chemotherapeutic agents. However, it seems to present some difficulties with regard to sensitivity, since evaluation is done by measurement of graft size. In this study, SRC was performed on six clinical cases of colorectal cancer using nude mice, which were given UFT 15 or 20 mg/kg orally or 2.5 mg/kg CDDP subcutaneously for 2-6 days. Histological changes in the grafted tumors were then observed by electron microscopy. Mucous granules and other features were assessed for evaluation of assay sensitivity. The number of mucous granules seemed to be the most reliable parameter that paralleled the sensitivity evaluated by tumor diameter. Other features such as nuclear mitosis, lysosomal increment and abnormal accumulation of ribosomes, had little correlation with sensitivity. However, further exploration is warranted with regard to local defects

of the cytoplasm. This ultrastructural examination suggested that grafted tumor cells were damaged slightly by implantation under the renal capsule, and that the SRC using tumor size as a parameter is clinically useful under conditions where the tumor xenografts show good viability and proliferation in the control group.

Answer 67:

Bibliographic Information

The role of additional chemotherapy with oral UFT in intravenous combination chemotherapy with cisplatin and 5-fluorouracil for human gastric cancer xenograft lines of well- and poorly- differentiated adenocarcinomas transplanted in nude mice. Tseng C C; Nio Y; Tsubono M; Kawabata K; Masai Y; Hayashi H; Fukumoto M; Tobe T First Department of Surgery, Kyoto University Faculty of Medicine, Japan Anticancer research (1992), 12(4), 1295-9. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1503424 AN 92368155 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In order to assess the role of maintenance chemotherapy with the oral anticancer agent UFT, a mixture of uracil and futraful, in the intensive intravenous chemotherapy for gastric cancer, nude mice transplanted with human gastric cancer xenografts were treated with intravenous 5-fluorouracil (5-FU) and cisplatin (CDDP), alone or in combination, with or without the oral anticancer agent UFT. UFT was given at its maximal clinical dose of 10 mg/kg of body weight daily for 2 weeks, while 5-FU and/or CDDP was intravenously administered at the dose of 20 mg/kg and 1.8 mg/kg of body weight respectively once a week, alone or in combination, for two weeks. The results revealed that 5-FU or CDDP alone were ineffective for both GC-YN, a well differentiated adenocarcinoma line, and GC-SF, a poorly differentiated adenocarcinoma line; however, UFT was effective for GC-SF. In combinations, only the three-agent combination 5-FU + CDDP + UFT (FPU) was effective for GC-YN; however, all the two-agent combinations and FPU were effective for GC-SF. FPU significantly suppressed the growth of GC-YN much more than all the other treatment groups. In contrast, although all combinations as well as UFT alone were effective for GC-SF, there was no significant difference among these effective groups. Moreover, no side effects were noted in combined use of UFT. This study suggests that oral UFT as a maintenance treatment may be beneficial in the combination chemotherapy for human gastric cancer.

Answer 68:

Bibliographic Information

Comparative studies on the antitumor activity of fluorinated pyrimidine derivatives against human bladder, cervical and ovarian cancer xenografts in nude mice. Miwa M; Sekiguchi F; Akaza H; Tokita H; Nitta K; Adachi S; Kanazawa K; Ishitsuka H Dept. of Oncology and Immunology, Nippon Roche Research Center, Japan Gan to kagaku ryoho. Cancer & chemotherapy (1991), 18(10), 1579-86. Journal code: 7810034. ISSN:0385-0684. (COMPARATIVE STUDY); (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 1831339 AN 91336740 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Fluorinated pyrimidines given orally were examined for their antitumor activity with 11 human cancer xenograft models (4 bladder, 4 cervical and 3 ovarian cancers). The drugs were evaluated to be effective when they inhibited tumor growth over 58%. UFT was not effective against all of 11 cancer xenografts tested. 5-Fluorouracil (5-FU) was effective against only one bladder cancer xenograft among 6 cancer xenografts tested. On the other hand, 5'-deoxy-5-fluorouridine (5'-DFUR) was effective against one bladder, 3 cervical and one ovarian cancer xenografts. The Antitumor activity of 5'-DFUR was correlated with the enzyme activity of pyrimidine nucleoside phosphorylase, which is an essential enzyme for phosphorolysis of 5'-DFUR to 5-FU.

Answer 69:

Bibliographic Information

Experimental combined chemo- and endocrine therapy with UFT and tamoxifen in human breast carcinoma xenografts serially transplanted into nude mice. Kubota T; Josui K; Ishibiki K; Abe O; Yamada Y; Asanuma F; Kawamura E; Koh J; Shiina E Department of Surgery, School of Medicine, Keio University Nippon Gan Chiryo Gakkai shi (1990), 25(12), 2767-73. Journal code: 7505713. ISSN:0021-4671. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2074386 AN 91162037 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We have investigated the experimental combined chemo- and endocrine therapy of UFT and tamoxifen (TAM) on two human breast carcinoma xenografts, R-27 and Br-10 with estrogen receptors (ER) serially transplanted into nude mice. When sc inoculated tumor started the exponential growth, the treatments were initiated in four groups which were control, UFT 20 mg/kg (as tegafur) po daily for 18 times, TAM 5 mg/kg im twice a week for 6 times and UFT + TAM groups. The antitumor activity of the agents were assessed by the growth curves, the lowest T/C ratios of the relative mean tumor weight and the actual tumor weights at the end of the experiments. TAM alone was effective on both R-27 and ineffective on Br-10, while UFT alone was ineffective on R-27 and Br-10. The combination antitumor activity was observed in R-27 but not in Br-10. When 5 mg of TAM per kg and 20 mg of UFT per kg as tegafur was administered daily po for 2 wk, there were no statistically significant differences between the concentration of 5-FU in UFT alone and UFT + TAM groups for the two strains. By the assay of ER and progesterone receptors using the same specimen, it was observed that ER was stable by the treatment of UFT, while ER was suppressed by the treatment of TAM in both tumor strains. In addition, this suppression of ER by TAM alone was enhanced by the combined treatment with UFT in both the strains.(ABSTRACT TRUNCATED AT 250 WORDS)

Answer 70:

Bibliographic Information

The effect of UFTM therapy on primary and metastatic colon cancer from the same human xenotransplanted into nude mice. Takahashi Y; Ohta T; Ooi A; Ogino T; Mai M Department of Surgery, Kanazawa University, Japan The Japanese journal of surgery (1990), 20(4), 406-10. Journal code: 1302176. ISSN:0047-1909. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2167403 AN 90355460 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Successful simultaneous transplants of a cancer of the ascending colon from a 60 year old woman, taken from 3 sites: the primary focus, a lymph node metastasis, and a hepatic metastasis, into nude mice yielded KHC (-P, -N, -H) strains. These three strains were compared under uniform conditions of nude mouse transplantation from the standpoints of morphological variation, growth rate, and sensitivity to chemotherapy. The results showed no major differences in morphology or growth rate. However, an effect on chemotherapeutic sensitivity was observed in KHC-P and KHC-N, with reduction rates of 25.8 per cent and 31.4 per cent, respectively, in the MMC only treatment group with large doses, and in KHC-N and KHC-H, with reduction rates of 46.5 per cent and 34.9 per cent, respectively, in the UFTM group. Chemotherapy sensitivity not only exhibited heterogeneity by site, but also differed according to the chemotherapeutic agent used. These results indicate that this method of nude mouse transplantation is a good experimental system for comparing primary foci and metastases under uniform conditions, and also strongly suggest the presence of heterogeneity in sensitivity to chemotherapy.

Answer 71:

Bibliographic Information

Experimental study of the effect of combined treatment of UFT with CDDP on human solid tumor-xenografts in nude mice. Yamada Y; Saito H; Oie S; Takechi T; Nakano K; Takeda S Biological Research Laboratory, Taiho Pharmaceutical Co., Ltd Gan to kagaku ryoho. Cancer & chemotherapy (1990), 17(7), 1327-31. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2114827 AN 90314427 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The effect of combined treatment of UFT with CDDP, especially the optimal time-dependent administration sequence, was studied in nude mice bearing nine human cancer xenografts derived from stomach, colon, lung, breast and uterocervical cancers following treatment with clinically equivalent doses and routes of administration. This combination treatment produced a higher response rate than a single treatment in 7 out of 9 cancers (78%). However, the combination timing of UFT and CDDP was assumed to be an important factor to produce a good therapeutic effect, since the combination effect was different by changing the treatment procedure, e.g., UFT followed by CDDP or CDDP followed by UFT. There was a low correlation between combination effect and the treatment procedure, origin of tissues, histology and doubling time of cancer cells or efficacy of a single agent. The strongest antitumor effect was observed by the treatment with UFT administered both prior to CDDP and after CDDP. Such treatment procedure seemed to be reasonable for cancers of unknown origin or character.

Answer 72:

Bibliographic Information

Analysis of the mechanism of increased antitumor activity of UFT after combined treatment with CDDP. Oie S; Okabe H; Takeda S; Yamada Y Biological Research Laboratory, Taiho Pharmaceutical Co., Ltd Gan to kagaku ryoho. Cancer & chemotherapy (1990), 17(7), 1321-6. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2114826 AN 90314426 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Previously we have reported the efficacy of the combination therapy of UFT with CDDP against several human cancer xenografts implanted in nude mice. Among all cell lines tested, KM20C (Human colon adenocarcinoma) has shown the most pronounced synergistic antitumor effect after administration of CDDP prior to UFT. The effect of CDDP administered after UFT and that of either drug alone were weaker. To clarify the mechanism of this synergistic effect, the change of the poolsize of reduced folate in KM20C, induced by CDDP treatment, was measured. The pretreatment with CDDP increased the poolsize of CH2-H4 folate and H4 folate and increased the binding of FdUMP to the dTMP synthase of an intact cells. Based on the above data, it was concluded that the enhancement of cell sensitivity to UFT was caused by the CDDP-induced increase of the reduced folate pool, in consequence leading a better binding of FdUMP generated from UFT to dTMP synthase, a target enzyme for the antitumor activity of fluorinated pyrimidines.

Answer 73:

Bibliographic Information

Relationship between antitumor activity and the inhibition of thymidylate synthase after oral administration of UFT in nude mice bearing human tumor. Fujita M; Fujita F; Uchida J; Takeda S; Yamada Y; Taguchi T Dept. of Surgery, Research Institute for Microbial Disease, Osaka University Gan to kagaku ryoho. Cancer & chemotherapy (1990), 17(4 Pt 1), 627-32. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article;

(JOURNAL ARTICLE) written in Japanese. PubMed ID 2108611 AN 90210639 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We studied the relationship between antitumor efficacy of UFT, which is a most widely used drug among fluorinated pyrimidines recently, and its effect on the content and the inhibition rate of thymidylate synthase (TS) in 15 human tumor xenografts derived from stomach, colon, breast and pancreatic cancer patients. There was a linear relationship between the content of TS and tumor mass doubling time (MDT). It may be shown that TS content reflects the growth rate of tumor cells. It should be stressed that tumor growth inhibition rate (TGIR), induced by UFT, correlated well with the inhibition of TS (TSI), particularly in the stomach and breast cancer. These results demonstrate that the measurement of inhibition rate of TS is important for the prediction and evaluation of clinical efficacy of UFT.

Answer 74:

Bibliographic Information

Anti-tumor effect of fluoropyrimidines on human tumor cell lines transplanted in nude mice with CCl4-induced liver dysfunction. Nio Y; Imai S; Shiraishi T; Ohgaki K; Tobe T First Department of Surgery, School of Medicine, Kyoto University, Japan Nippon Geka Gakkai zasshi (1989), 90(4), 538-45. Journal code: 0405405. ISSN:0301-4894. (COMPARATIVE STUDY); (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2503704 AN 89343923 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Tegafur (FT) is a masked compound of 5-fluorouracil (5-FU) and supposed to be activated in the liver. The present study was designed to estimate anti-tumor effect of FT on human tumors transplanted in nude mice with liver dysfunction induced by CCl4. Histologically, cirrhotic changes of liver were observed after injection with 1ml/kg 10% CCl4 twice a week for 8 weeks. Mice were transplanted with human gastric (GC-SF) or colonic cancer (CC-ZK) lines, and daily administered intragastrically with 5-FU (15mg/kg), FT (100mg/kg) or UFT (FT 20mg/kg + Uracil 44.8mg/kg) for 4 weeks. The growth of GC-SF was enhanced by liver dysfunction, but that of CC-ZK was not affected. The mean growth inhibition rates (MGIR) of CC-ZK by 5-FU, FT or UFT were 18.3, 33.1 and 54.2%, respectively, in mice without liver dysfunction, and 14.0, 50.0 and 59.5%, respectively, in mice with liver dysfunction. The MGIRs of GC-SF were 39.0, 63.8 and 48.0%, respectively, in mice without liver dysfunction, and 12.6, 53.6 and 50.0%, respectively, in mice with liver dysfunction. In both lines effect of 5-FU was reduced in liver dysfunction, but those of FT and UFT was not. These results suggest that FT and UFT can be used for cancer patients with liver dysfunction.

Answer 75:

Bibliographic Information

Level of 5-fluorouracil in cancerous and normal tissues of nude mice bearing human endometrial carcinoma after administration of UFT coadministered with nicardipin. Suzuki M; Sekiguchi I; Tamada T; Nishida M Nippon Gan Chiryo Gakkai shi (1988), 23(11), 2703-8. Journal code: 7505713. ISSN:0021-4671. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3150425 AN 89256987 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 76:

Bibliographic Information

The antiproliferative effects of fluoropyrimidine derivatives against human tumor xenografts in a subrenal capsule assay. Nishiyama M; Takagami S; Kirihara Y; Saeki T; Hirabayashi N; Nosoh Y; Niimoto M; Hattori T Department of Surgery, Hiroshima University, Japan The Japanese journal of surgery (1988), 18(6), 725-8. Journal code: 1302176. ISSN:0047-1909. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2977626 AN 89236816 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antiproliferative effects of the fluoropyrimidine derivatives, 5-fluorouracil (5-FU), 1-(2-tetrahydrofuryl)-5-fluorouracil (Tegafur), UFT, 1-hexylcarbamoyl-5-fluorouracil (HCFU), and 5'-deoxy-5-fluorouracil (5'DFUR), were investigated in a 4 day subrenal capsule assay. The antiproliferative effects against two human tumor xenografts established in athymic mice were examined after treatment with three different doses of each anticancer agent, and the adequate dose of each anticancer agent in this experimental system was estimated as: 473 mg/kg for Tegafur, 433 mg/kg for UFT, 50 mg/kg for HCFU and 185 mg/kg for 5'DFUR, respectively. A comparative study of the antiproliferative effects of fluoropyrimidine derivatives was carried out against 7 xenografts. According to our criteria of positive tumor response, the effective rates were: 1 of 7 (14.3 per cent) by 5-FU, 2 of 7 (28.6 per cent) by Tegafur, 2 of 7 (28.6 per cent) by UFT, 1 of 6 (16.7 per cent) by HCFU, and 1 of 4 (25.0 per cent) by 5'DFUR, respectively. Although no statistical differences were demonstrated between the agents, the utility of a chemosensitivity test before clinical use was suggested.

Answer 77:

Bibliographic Information

Treatment of established human renal cell carcinoma--experimental treatment with interferon and UFT. Onishi T; Iizuka N; Suzuki M; Mori Y; Kondo I; Nakada J; Masuda F; Machida T Nippon Gan Chiryo Gakkai shi (1988), 23(7), 1498-502. Journal code: 7505713. ISSN:0021-4671. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in Japanese. PubMed ID 3141533 AN 89035733 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 78:

Bibliographic Information

Effect of UFTM therapy on primary and metastatic colon cancer of human xenotransplanted in nude mice. Takahashi Y; Ohta T; Mai M Dept. of Surgery, Cancer Research Institute, Kanazawa University Gan to kagaku ryoho. Cancer & chemotherapy (1988), 15(9), 2815-7. Journal code: 7810034. ISSN:0385-0684. Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3137893 AN 88325534 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 79:

Bibliographic Information

Combined effects of UFT with other anticancer agents using in vivo chemosensitivity tests. Nishiyama M; Niimi K; Takagami S; Hirabayashi N; Yamaguchi M; Saeki T; Yoshinaka K; Wang D C; Niimoto M; Hattori T Department of Surgery, Research Institute for Nuclear Medicine and Biology, Hiroshima University, Japan The Japanese journal of surgery (1988), 18(1), 93-7. Journal code: 1302176. ISSN:0047-1909. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 3133515 AN 88259830 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In order to estimate the combined effects of UFT with other anticancer agents, a nude mouse experimental system (NMES), and a subrenal capsule assay (SRCA) were investigated. Three human tumor xenografts were serially transplanted into nude mice and examined. These were; EH-1 established from esophageal cancer, SH-6 from gastric cancer and CH-3 from colon cancer. The antiproliferative effects were estimated in accordance with the NCI therapeutic protocol. Significant antiproliferative effects were obtained only in NMES and a positive relationship was observed between the two assays (p less than 0.05). In the groups which were treated with a single agent, positive tumor responses were observed against mitomycin C in SH-6, against cis-DD platinum in SH-6 and EH-1, and against adriamycin in EH-1, respectively. On this study the synergistic, additive and subadditive effects were defined as the positive combined effects. The combination of MMC and UFT produced positive combined effects for all xenografts in both assays.

Answer 80:

Bibliographic Information

Anti-tumour effect of UFT on human renal cell carcinoma heterotransplanted into nude mice. Onishi T; Machida T; Masuda F; Furuta M; Kondo I; Iizuka N; Suzuki M; Mori Y; Nakada J Dept. of Urology, Jikei University School of Medicine Gan to kagaku ryoho. Cancer & chemotherapy (1988), 15(5), 1721-6. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3130807 AN 88221281 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

1) Using two histologically different human renal cell carcinomas heterotransplanted into nude mice, the antitumour effect of UFT was investigated, and an attempt was made to analyze the properties of the tumour strains where a drug efficacy was noted. 2) The two strains used were the JRC 1 strain (tumour doubling time of 9.4 days, clear cell type, papillary histologic pattern, grade 3) and the JRC 11 strain (tumour doubling time of 2.72 days, granular cell type, anaplastic histologic pattern, grade 4). 3) Two dose groups were set up, one receiving 10 mg/kg of tegafur (FT) and 22.4 mg/kg of uracil and the other receiving 20 mg/kg of FT and 44.8 mg/kg of uracil. Each group was further divided into an early administration group (start of administration 3 days after the tumour transplantation) and a late administration group (start of administration at a time when the transplanted tumour proliferated to weight of 100 to 300 mg). 4) Effect as noted in the tumour proliferation inhibition rate was seen only in the group receiving 20 mg/kg of FT and 44.8 mg/kg of uracil in both early and late administration groups of the JRC 1 strain. Among these groups only the early administration groups showed a histological positive effect. 5) The fact that the measured 5-FU intra-tumour concentration in the JRC 1 strain was only 1/4 that of the JRC 11 strain demonstrates more susceptibility of JRC 1 strain to UFT. Moreover, intratumoral concentration of 5-FU differed markedly even with the same administration method and dosage level. This result indicates that intra-tumour concentration will be different if the histological pattern differs.

Answer 81:

Bibliographic Information

Combination chemotherapy with cisplatin and UFT malignant tumors of the head and neck--experimental study of human nasopharyngeal carcinoma (A2L/AH) xenografted to nude mice. Furukawa M; Ohoka H; Kamide M; Umeda R Dept. of Otorhinolaryngology, School of Medicine, Kanazawa University Gan to kagaku ryoho. Cancer & chemotherapy (1988), 15(2), 301-5. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3124770 AN 88132947 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Combination therapy with cis-platinum (CDDP) and UFT was examined with human nasopharyngeal carcinoma (A2L/AH)

implanted in nude mice. The tumor growth of A2L/AH was inhibited in the group administrated UFT 20mg/kg, but was not in 10mg/kg group in comparison with the control group. An inhibition rate (IR) of the tumor growth was 80.2 and 21.3% respectively. The group received CDDP (5mg/kg, q7d X 3, 2mg/kg, q7d X 3 and 1 mg/kg, qd X 6) by i. p. injection, resulted in 75.2, 37.4 and 23.1% inhibitions respectively. While, the response rate in the group treated with CDDP (1 mg/kg, qd X 6) and UFT (10mg/kg) showed a synergistic effect (IR; 66.3%) which was higher than in the group administrated CDDP (2mg/kg, q7d X 3) and UFT (10mg/kg) (IR; 58.3%).

Answer 82:

Bibliographic Information

Antitumor effect of intermittent oral administration of UFT against human rectal cancer xenografted in nude mice. Yamada K; Takao S; Ishizawa T; Shimazu H 1st Dept. of Surgery, Kagoshima University School of Medicine Gan to kagaku ryoho. Cancer & chemotherapy (1988), 15(2), 291-6. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3124769 AN 88132945 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Effect and toxicities of oral administration of UFT were examined with tumor xenografts (COK-7LiM) in nude mice. Special attention was paid to the differences between daily (Q1D X 9) and intermittent (Q4D X 3) treatments with this agent. The optimal doses of UFT were determined on the basis of the maximal tolerated dose of the agent in nude mice. It was remarkable that the chemotherapeutic effect by intermittent administration of UFT showed a significantly better result than that by daily administration. No difference was seen in the toxicities between the two methods of administration of UFT. Moreover, the concentration of 5-FU in the tumor tissue treated with UFT intermittently was significantly higher than that by daily administration method.

Answer 83:

Bibliographic Information

Tegafur and 5-FU concentrations in cancerous and normal tissues in nude mice after oral administration of UFT. Murahashi I; Honda M; Mukae K; Hosoya Y; Takasaki E Dept. of Urology, Dokkyo University School of Medicine, Tochigi, Japan Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(12), 3265-9. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3120643 AN 88075980 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Tegafur and 5-fluorouracil (5-FU) concentrations in blood, tumor, kidney and liver tissues of nude mice implanted with human urogenital carcinoma were determined after oral administration of UFT. The results were as follows: The concentration of tegafur in serum and other tissues rose quickly reading to the peak levels by 15 minutes after administration of UFT, then decreasing gradually. The concentration of 5-FU in serum, liver and kidney showed similar changes, but concentration of tumor tissues were maintained high until 2 hours after administration. These results suggest that coadministration of uracil with tegafur increase the antitumor activity of tegafur.

Answer 84:

Bibliographic Information

Effect of combination of UFT and MMC (UFT-M therapy) on human colonic cancer xenotransplanted into nude

mice. Takahashi Y; Kikuchi R; Ueno M; Mai M Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(5 Pt 1), 1345-7. Journal code: 7810034. ISSN:0385-0684. Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3107480 AN 87212081 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 85:

Bibliographic Information

In vivo chemosensitivity test for UFT and FT-207. II. Chemosensitivity test on human tumor xenografts transplanted in nude mice. Niimi K; Nishiyama M; Hirabayashi N; Yamaguchi M; Nosoh Y; Wang D C; Toge T; Niimoto M; Hattori T Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(5 Pt 1), 1281-5. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3107479 AN 87212070 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The present study was designed to predict the clinical effect of UFT and FT-207 in short-term administration using a nude mouse-xenograft system. Five human tumor xenografts transplanted into nude mice were used. UFT and FT-207 were administered with the LD10 doses orally for seven consecutive days. Tumor size was measured on day 7, 14 and 21 after the administrations. No significant differences in antiproliferative effects were observed between the measurements of tumor size made on day 7 and day 21. UFT inhibited significantly the tumor growth of CH-I established from colon cancer in which the prolongation of life span has been obtained by clinical long-term administration of UFT. These results suggest that this chemosensitivity test system using nude mice is useful for prediction of clinical response at 7 days after final administration of UFT and FT-207.

Answer 86:

Bibliographic Information

Combination chemotherapy with 3 or 4 drugs on human breast and gastrointestinal cancer xenografts in nude mice (II). Fujita F; Fujita M; Sakamoto Y; Shimozuma K; Inaba H; Taguchi T Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(5 Pt 1), 1252-9. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2953310 AN 87212065 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Because of the limited effects of single-agent chemotherapy for solid tumors, combination therapy was employed in an attempt to enhance the clinical effects. Following our former report in which the combination effects of mitomycin C (MMC) and 5'-deoxy-5-fluorouridine (5'-DFUR) were clarified, combined applications of 4 drugs, vindesine (VDS), methotrexate (MTX), cisplatin (CDDP) and 5'-DFUR against 3 lines of human breast cancer (H-62, H-31, H-71), and one line each of gastric cancer (H-55) and colon cancer (H-110) xenografted into nude mice were evaluated in comparison with CAF (cyclophosphamide, adriamycin and 5-FU) therapy which is commonly used for breast cancer. Treatment was initiated in groups of 7 mice each when the mean tumor volume of subcutaneous tumors had reached about 100mm3, and the therapeutic effect was evaluated in terms of the inhibition rate (I.R.). A synergistic effect is said to exist when the combination therapy is superior to each single drug therapy at the maximal tolerated dose. Combination therapy with 3 drugs (VDS, CDDP and 5'-DFUR) or 4 drugs (VDS, CDDP, MTX and 5'-DFUR) achieved an I.R. of over 98%, i.e., a marked effect with tumor shrinkage, in 3 lines of tumors (H-55, H-31 and H-62). Moreover, remarkable effects were shown even in the other 2 lines which were insensitive to every single-agent therapy, the I.R. values being 85.7% (H-71) and 78.5% (H-110). A synergistic effect was obtained in 3 of the 5 lines examined. These combination therapies were histologically superior to therapies employing each single-drug therapy or CAF therapy. The side effects for combination of these 3 or 4 drugs evaluated by body weight loss were transient and equivalent to maximal dose of VDS or CDDP. Clinically, it is thought that these combined therapies of 3 or 4 drugs will bring about a considerable response in practice.

Answer 87:

Bibliographic Information

Combination cancer chemotherapy of human gastric and colon carcinomas in nude mice--sequential cancer chemotherapy involving mitomycin C and tegafur. Kubota T; Ishibiki K; Abe O Gan to kagaku ryoho. Cancer & chemotherapy (1986), 13(4 Pt 1), 938-44. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3083789 AN 86185585 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Three human tumor xenografts serially transplanted into nude mice were used for an experimental combination cancer chemotherapy consisting of mitomycin C (MMC) and tegafur (FT-207). The strains used for the experiments were two gastric (St-4 and St-15) and one colon (Co-3) carcinomas. The minimal effective doses of MMC were administered i. p. 24h after the s. c. tumor inoculations followed by 60 mg/kg of FT-207 in the three different modalities i. p. These were (A) daily administration of FT-207, (B) FT-207 only, 24h after MMC treatment and (C) FT-207 only, 5 days after MMC treatment. The antitumor effect assessed by the tumor weight at the end of the experiment was found to be (A) divided by (B) greater than (C), whereas the total administration doses of FT-207 were (A) greater than (B) = (C). As this result suggested the significance of FT-207 given 24h after MMC, flow cytometric analysis of St-15 tumor was conducted 24 and 48 h after the MMC treatment. It was observed that the incidence of 2n cells was depressed and the amount of 4n cells increased by MMC, indicating the recruitment of tumor cells into the proliferating phase. Because these recruited cells were thought to be sensitive to FT-207, it was supposed that the antitumor effect was elevated when FT-207 was given 24h after MMC. This semi-synchronized combination cancer chemotherapy involving MMC and FT-207 might therefore be useful for clinical application.

Answer 88:

Bibliographic Information

Ultrastructural effects of alpha and gamma interferons and cytostatics on ovarian cancer cells in the subrenal capsule assay (SRCA). Soderstrom K O; Maenpaa J; Cantell K; Kangas L; Gronroos M Annales chirurgiae et gynaecologiae. Supplementum (1985), 199 38-43. Journal code: 7702959. ISSN:0355-9874. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 3933399 AN 86049165 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Ovarian cancers from 9 patients were grown in the subrenal capsule assay for 6 days. Groups of five mice were treated with saline, alpha interferon, a combination of alpha and gamma interferons and 2 cytostatic drug combinations with and without alpha interferon. The histological evaluation suggested that the regression of drug-treated transplants measured with stereomicroscope can reliably be used as an indicator of drug effect. However, it is possible that in a few cases the control growth measured with preparation microscope is somewhat exaggerated due to inflammatory reactions induced by the grafts. At the ultrastructural level, the cell, nuclear and mitochondrial volumes were morphometrically evaluated. The cytostatic treatment caused marked degenerative changes with nuclear enlargement and cytoplasmic vacuolization of the tumour cells. Only small differences could be detected between the control groups and the interferon-treated groups. In these groups, the nuclear and cytoplasmic volumes were not significantly different, whereas the mitochondrial volume was larger in the interferon-treated cells.

Answer 89:

Bibliographic Information

Enhanced accumulation of 5-fluorouracil in human tumors in athymic mice by co-administration of Ftorafur and uracil. Tang S G; Hornbeck C L; Byfield J E International journal of radiation oncology, biology, physics (1984), 10(9), 1687-9. Journal code: 7603616. ISSN:0360-3016. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 6434499 AN 85006496 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Human colonic tumors grown in athymic mice were tested for the effect of coincident uracil (U) and Ftorafur (FT) exposure versus FT alone on 5-Fluorouracil (5-FU) metabolism. Serum and tumor FT and 5-FU levels were studied as a function of time after FT +/- U injections. The combination of U + FT led to significantly higher tumor/serum 5-FU ratios than FT alone. The data indicate that the metabolism of 5-FU released from FT can be modulated by coincident U exposure in human tumor cells in vivo. Such combinations may be of use in the development of oral 5-FU pro-drugs for applications using 5-FU as an out-patient non-invasive radiosensitizer.

Answer 90:

Bibliographic Information

Effects of 5'-deoxy-5-fluorouridine on human gastrointestinal and breast cancers xenografted to nude mice. Fujita F; Fujita M; Taguchi T Gan to kagaku ryoho. Cancer & chemotherapy (1984), 11(8), 1635-43. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in Japanese. PubMed ID 6236751 AN 84305913 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

As a preclinical secondary screening trial, the efficacy of a new derivative of 5-fluorouracil, 5'-deoxy-5-fluorouridine (5'-DFUR), on 15 human cancers xenografted serially to nude mice of BALB/c background was evaluated in comparison with two other derivatives, tegafur and UFT. Oral administration of 123 mg/kg/day of 5'-DFUR, 25-30 times, produced effective inhibition in 5 out or 7 gastric cancers, 2 out of 3 colorectal cancers, all 3 of breast cancers and 1 out of 2 pancreatic cancers, totalling 11 out of 15 cancer lines (73%) examined. In some cases shrinkage of tumors was noted without any noticeable side effects. Although an increased dose of 185 mg/kg/day of 5'-DFUR resulted in more prominent inhibition on all 9 tumors tested, some animals suffered from severe loss of body weight or diarrhea. Comparative experiments with of equimolac doses of 5'-DFUR(123 mg/kg) and FT-207(100 mg/kg) showed that the inhibition rate of the former was higher than that of the latter in all 8 lines of cancers examined. Six experiments in particular (2 gastric, 1 colorectal, 2 breast and 1 pancreatic cancers), showed that 5'-DFUR statistically sustained more effective suppression. Direct comparisons of 5'-DFUR and UFT were also made in 5 experiments in which 3 cancers were more sensitive to the former drug. Promising results in clinical trials can be expected with the new drug 5'-DFUR for these kinds of cancers.

Answer 91:

Bibliographic Information

Experimental chemotherapy of human gastrointestinal and breast cancers in nude mice and its correlation to clinical effect. Fujita M; Fujita F; Taguchi T Gan no rinsho. Japan journal of cancer clinics (1984), 30(9 Suppl), 1168-74. Journal code: 1257753. ISSN:0021-4949. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in Japanese. PubMed ID 6433068 AN 84292855 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

For evaluating the predictive value of experimental chemotherapy of human cancers xenografted to nude mice, two types of comparison between experimental responses in nude mouse system and their clinical results were made. The responses of 12 experimental therapies with single agent or drug combination were directly compared with those of the same kinds of therapy in each donor patient. Satisfactory agreement between the two results was shown in every comparison, with 3 true positives and 9 true negatives. Using 15 human cancer lines consisting of 7 gastric, 3 colorectal, 2 pancreatic and 3 breast cancers, single agent treatment with 6 drugs (MMC, ADR, ACNU, FT-207, 5'-DFUR) were performed. The effectiveness of each drug to these xenografts was in good accordance with the known clinical effect of each drug in the same type of cancer. Nude mouse-human cancer panel is useful for the secondary screening of the new drug.

Answer 92:

Bibliographic Information

Relationship of chemotherapy on human cancer xenografts in nude mice to clinical response in donor patient. Fujita M; Hayata S; Taguchi T Journal of surgical oncology (1980), 15(3), 211-9. Journal code: 0222643. ISSN:0022-4790. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 6776350 AN 81050749 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Responsiveness of experimental chemotherapy on human cancer xenografts in nude mice was directly compared with clinical response to the same chemotherapy in their donor patients. These xenografts were 1 line of rectal cancer (H-26), two lines of gastric cancer (H-08 and H-22), and 1 line of breast cancer (H-62). Experimental chemotherapies studied were single-drug FT-207 to four lines of xenografts and a combination of mitomycin C, 5-FU, and cytosine arabinoside (MFC) to a line of gastric cancer H-08. Single-drug treatment with FT-207 to H-26 resulted in remarkable retardation of the tumor growth. The comparative treatment with FT-207 suppository to the donor patient of H-26 showed appreciable response. All the other chemotherapies to three other lines (H-08, H-22, and H-62) induced no significant response, which was parallel to the corresponding clinical response in each donor patient. The sensitivity to chemotherapeutic drugs was thought to be still preserved in human cancer xenografts in nude mice.